A New Technological Era for American Agriculture

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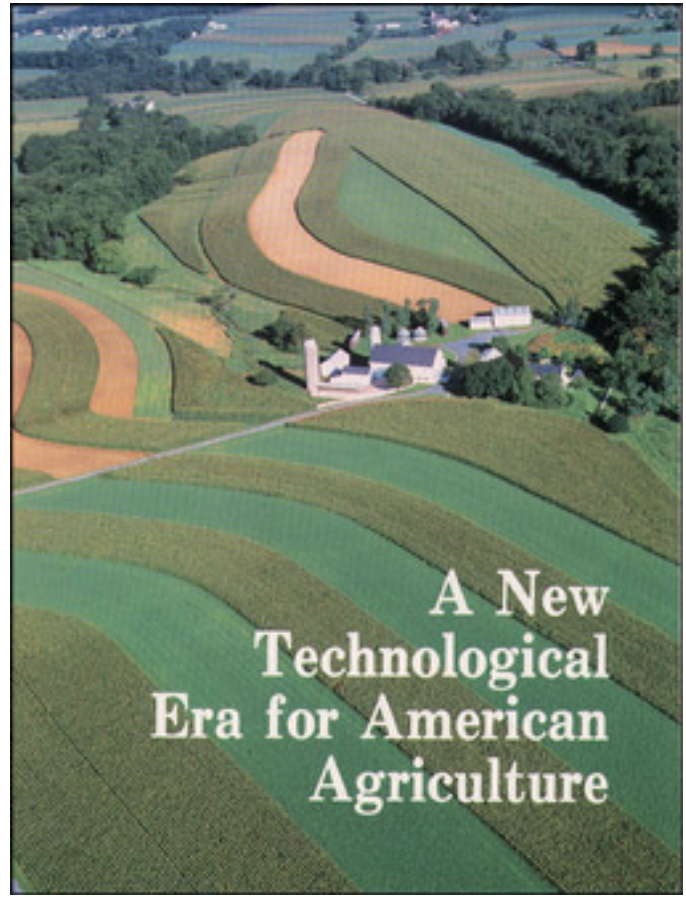

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Foreword

American agriculture is entering a new technological era that holds great promise. Biotechnology and advanced computer systems have the potential to increase productivity, enhance the environment, improve food safety and quality, and bolster U.S. agricultural competitiveness.

Many of these new technologies will be available in the 1990s. But their introduction will be under circumstances unlike any met by past technologies. Uncertainties over these new technologies raise questions of potential impacts on food safety and the environment, and possible economic and social costs. Nevertheless, there will be a push for some of these technologies-biotechnology in particular—to be used commercially, adopted by industry, and accepted by the public.

Congress requested the Office of Technology Assessment to examine emerging technologies that may be available to American agriculture in the 1990s, their potential for industry, and consequent policy issues. This report analyzes the technologies and related policy issues Congress may need to resolve. The analysis includes an assessment of adjustments industry must make to capitalize on the new technologies, the scientific and institutional issues relevant to food safety and environmental risk and benefit, and the implications for intellectual property rights and science policy.

The report concludes that these technologies have the potential to provide new solutions to many agricultural problems. The challenge, however, will be whether government, industry, and the public can strike the proper balance of direction, oversight, and use to allow these technologies to flourish. Congress will be faced with many issues and choices as American agriculture moves into this new era.

This OTA report for Congress is the fourth and final report in a series begun in 1990. The study was requested by the Senate Committee on Agriculture, Nutrition, and Forestry; the House Committee on Government Operations; and the House Committee on Agriculture. The first report issued was *Agricultural Research and Technology Transfer Policies for the 1990s, the* second report was *U.S. Dairy Industry at a Crossroad: Biotechnology and Policy Choices,* and the third report was *Agricultural Commodities as Industrial Raw Materials.* Findings from these reports were relevant to the issues debated for the 1990 Farm Bill.

OTA greatly appreciates contributions of the advisory groups, authors of background papers, reviewers, and other contributors to this study who were instrumental in defining key issues and a range of perspectives on them. Their participation does not necessarily represent endorsement of this report, for which OTA bears sole responsibility.

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NOTE: OTA appreciates and is grateful for the valuable assistance and thoughtful critique by the advisory group members. The groups do not, however, necessarily approve, disapprove, or endorse this report. OTA assumes full responsibility for the report and the accuracy of its contents.

Chapter 1

Overview and Summary

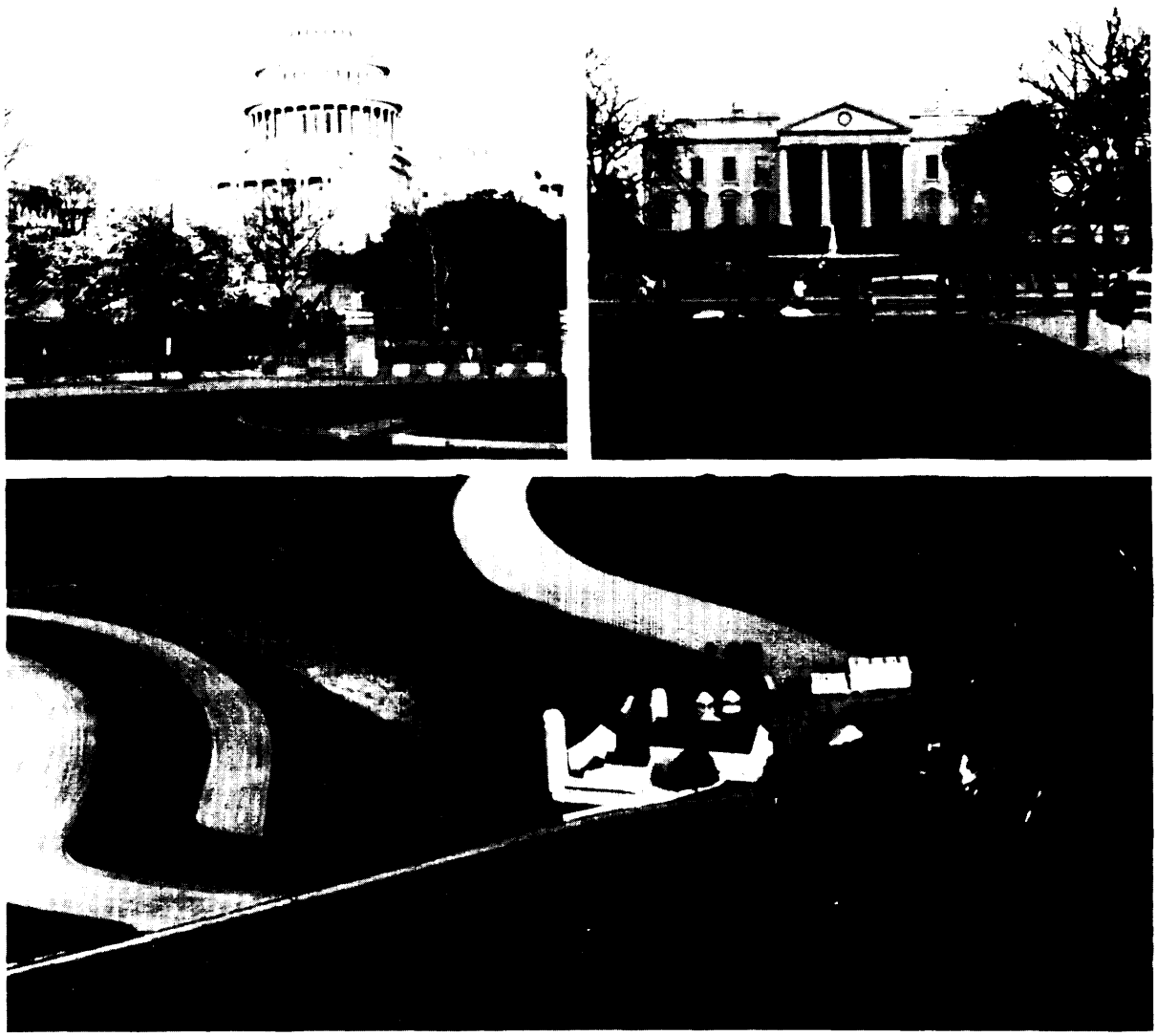

Photo credit: Grant Hellman, inc.

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Overview and Summary

Technological innovation has played a significant role in transforming American agriculture in the past and again promises major impacts on the U.S. food production and processing industries. The transition from horsepower to mechanical power (1920– 1950) boosted the productive capacity of agriculture even as farm labor requirements decreased dramatically. From 1950 to 1980 agricultural productivity rose further as chemical fertilizers, feed additives, and pesticides increased yields and helped farmers control pests and disease. Biotechnology and advanced computer systems now are ushering American agriculture into a new technological era. These technologies have the potential to increase U.S. agricultural productivity and competitiveness, enhance the environment, and improve food safety and quality.

Many of the new technologies will be commercially viable in the 1990s. However, they will not automatically be put to use. Today's public increasingly questions whether technological change is always good or needed and is voicing new concerns about the safety of the food supply, the environment, and the changing structure of agriculture. These issues as well as declining public confidence in institutions create an atmosphere in which agricultural biotechnology may not readily be approved for commercial use or adopted by industry. Lack of public acceptance could prevent some technologies from being used even if they are approved by regulatory agencies. To avoid this fate, agricultural biotechnology must meet rigorous scientific standards of safety and efficacy. And, institutions regulating these products must satisfy unprecedented demands for accountability.

This report focuses on the new technologies for agriculture and the related issues that policy makers most likely will face during this decade. Part I identifies advances being made in agricultural biotechnology for crops, animals, and food processing, and in computer technologies to improve agricultural management. Part 11 analyzes ways in which these technologies might improve agricultural productivity and discusses certain adjustments that industry will need to make to capitalize on this potential. Part 111 considers scientific and institutional issues relevant to environmental benefit and risk assessment of biotechnology. Part IV focuses on food safety and quality issues, presenting institutional, scientific, and public perspectives on these issues. Finally, Part V analyzes some of the implications of the technologies for intellectual property rights and science policy.

ADVANCING TECHNOLOGIES FOR AGRICULTURE

Biotechnology

Biotechnology, broadly defined, includes any technique that uses living organisms or processes to make or modify products, to improve plants or animals. or to develop microorganisms for specific uses. It rests on two powerful molecular genetic tools: recombinant deoxyribonucleic acid (rDNA); and cell fusion technologies. Using these techniques, scientists can isolate. clone, and study the structure of an individual gene and explore the gene's function. Such knowledge and skills allow scientists to exercise new control over biological systems, leading to significant improvements in agricultural plants and animals.

Plant Technologies

Each year in the United States, weeds, insects, and disease (as well as weather and soil conditions) significantly decrease potential crop yields and cost farmers billions of dollars in lost revenues. New approaches to control pests include the use of biological agents to manage pests and the application of biotechnology to produce plants with new genetic characteristics.

Biological control of pests is the use of living natural enemies to reduce pest populations to levels lower than would otherwise occur. The classical (searching native lands for control agents to pests of foreign origin) and augmentation (periodic release of control agents to increase populations) approaches are the most commonly used biological control tactics. To date, biological control has been most successfully used in orchards and vegetables; efficacy in field crops has been 'limited. Insect and weed control using biological control agents has been most successful; use of biological agents to control disease is lagging. Traditional selection and breeding approaches, as well as new biotechnology approaches are being used to improve the control and range of biological control agents. Several biocontrol agents currently are available or could be in the next 10 years, but the field is not sufficiently advanced to replace most pesticides in that time.

New tissue culturing and genetic engineering tools combined with traditional agricultural research methods are allowing scientists to alter plants to have greater dis-

ease, insect, and weed resistance; to withstand environmental stresses such as cold, drought, and frost; to develop value-added products from agricultural commodities; and to improve understanding of plant resistance and of the interactions of plants, pests, and biological control agents in the agro-ecosystem.

Genetic Engineering of Plants for Insect Control— Traditional breeding programs have and will continue to produce insect-resistant or insect-tolerant varieties of crops. However, the tools of biotechnology can be used to selectively engineer plants for this trait. Candidate genes must code for proteins that are stable in the plant cell and insect midgut; have high activity against target insects; and are safe for non-target invertebrates and animals. Genes coding for trypsin inhibitors and for bacterial Bacillus thuringiensis (Bt) toxin are two possible candidates. The gene coding for the Bt toxin has been cloned and inserted into plants; transgenic plants producing Bt toxins are expected to be commercially available by the mid to late 1990s.

Genetic Engineering of Plants for Weed Control— Improved understanding of the mechanisms of action of herbicides is leading to the improved ability to design herbicides effective against some plants (target weeds) but inactive against others (nontarget weeds or crops). The lack of naturally occurring resistance genes in crops limits the ability to use traditional breeding methods to develop herbicide tolerant crops; however genetic engineering techniques can overcome these constraints. The first herbicide tolerant crops are expected to be available commercially by the mid 1990s.

Photo credit: Richard Nelson, Samual Roberts Noble Foundation

Transgenic tomato plant expressing the coat protein gene of tobacco mosaic virus (left) and control plant (right).

Genetic Engineering of Plants for Disease Control— Biotechnology is being used to elucidate the mechanisms by which pathogenic organisms cause disease and to engineer plants with enhanced disease resistance. Genes coding for virus coat proteins (i. e., the proteins that make up the shell that surrounds viruses) can be genetically engineered into plants to elicit resistance to infection by the source virus, and in some cases to related viruses having similar coat proteins. Several plant viral coat proteins have been transferred to plants to confer resistance.

Genetically engineered dicotyledonous plants resistant to certain viruses are expected to be available commercially by the mid 1990s. But virus resistant monocotyledonous plants will probably not be available until the late 1990s or early 21st century. Plants resistant to bacteria and fungi are not expected to be developed until the end of the decade and not available commercially until after the year 2000.

Animal Technologies

Biotechnology has the potential to improve feed efficiency, reduce losses from disease, and increase reproductive success in all sectors of the livestock industry. Advances in growth promotants, reproductive technologies, and animal health will play a major role in enhancing the efficiency of animal agriculture and the quality of its products.

Growth Promotants-Currently used growth promotants such as anabolic steroids and antimicrobial compounds will continue to be used in the livestock sector. However, rDNA techniques are being used to produce new products such as a new class of protein hormones called somatotropins.

Porcine Somatotropin—Pigs administered porcine somatotropin (pST) for a period of 30 to 77 days show increased average daily weight gains of approximately 10 to 20 percent, improved feed efficiency of 15 to 35 percent, decreased adipose (fat) tissue mass and lipid formation rates of as much as 50 to 80 percent, and concurrently increased protein deposition of as much as 50 percent without adversely affecting the quality of the meat. Prolonged release formulations and daily injection produced similar growth rates and feed efficiencies. PST is currently being reviewed by Food and Drug Administration (FDA) for commercial use.

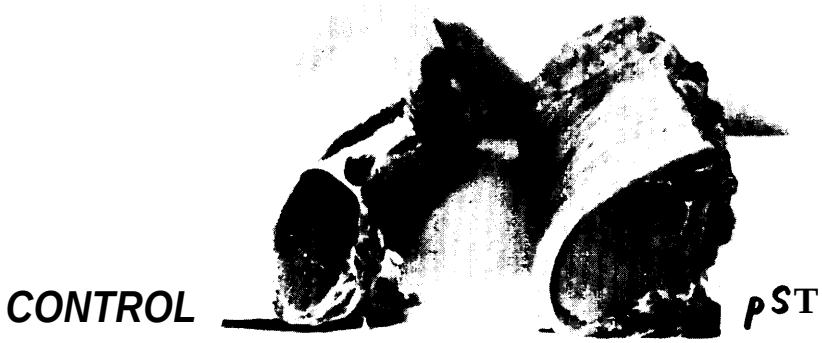


Photo credit: Terry Etherton, Pennsylvania State *University*

Comparison of pork loins that show the effect of pigs treated with porcine somatotropin (pST). The loin-eye area of the loin treated with pST is *8* square inches; the control is *4.5* square inches.

Bovine Somarotropin—Bovine somatotropin (bST) is currently undergoing FDA review for use in lactating dairy cows to increase milk production. While individual gains rely on the management ability of the producer, on average, gains of about 12 percent are reasonable. Bovine somatotropin does not alter the composition of milk. The fat, glucose, protein, mineral, and vitamin composition of milk fall within the range of values normally observed in milk from cows not supplemented with bST. Bovine somatotropin decreases pregnancy rates (proportion of cows becoming pregnant), increases days open (days from parturition to conception), but does not alter conception rates (services per conception). These observed effects are similar to those occurring in high-producing cows that do not receive bST. Implications of using bST in dairy production are discussed more thoroughly in the OTA publication U.S. *Dairy Industry at a Crossroad: Biotechnology and Policy Choices.*

Reproduction Technologies—The field of animal reproduction is undergoing a scientific revolution. For example, in the cattle industry it has become possible to induce genetically y superior females to shed large numbers of eggs (superovulation); and to fertilize these eggs in vitro with the sperm of genetically superior males. Each resulting embryo can then be sexed and split to produce multiple copies of the original embryo. Each of these new embryos can then be frozen for later use, or transferred to a recipient cow whose reproductive cycle has been synchronized to accept the developing embryo. The recipient cow carries the embryo to term and gives birth to a live calf. It may be possible in the near future to sex the sperm rather than the embryo, and to create more copies of each embryo than currently is possible. New techniques being developed will make it easier to insert new genes into the embryos to produce transgenic animals. Embryos produced by new reproductive methods are being marketed, although as yet no transgenic animals are available.

Transgenic Animals—The combination of new reproductive technologies with recombinant DNA technologies (the identification. isolation, and transfer of selected genes), provides opportunities to produce transgenic animals efficiently and cost effectively, and to improve livestock quality more rapidly than could be done with traditional breeding. Some transgenic livestock may contain genes that improve growth characteristics or resistance to disease. These new developments also have human medical implications. It may be feasible to produce important human pharmaceuticals in livestock. Transgenic animals can also serve as a powerful research tool to understand genetic and physiological functions, and to provide a model system to study human disease. For example, pigs display striking physiological similarities to humans and because of this, transgenic pigs are currently being developed to serve as a model system to understand and treat gastrointestinal cancers. Commercial availability of transgenic animals is not expected before the year 2000.

Animal Health Technologies—improvements in animal health will lead to considerable cost savings to the animal industry. Biotechnology rapidly is acquiring a prominent place in veterinary medical research. New vaccines include those created by deleting or inactivating

the genes in a pathogen that cause disease. The first gene-deletion viral vaccine to be approved and released for commercial use was the pseudorabies virus vaccine for swine.

Many currently used diagnostics tests are costly, time consuming, and labor intensive, and some still require the use of animal assay systems. Monoclinal antibodies and nucleic acid hybridization probes can be used to produce simpler, easily automated, and highly sensitive and specific diagnostic procedures. At least 15 different rapid diagnostic tests based on monoclinal antibodies are on the market or soon will be.

Food Processing Technologies

Historically, the food processing industry has had to accept and adapt to heterogeneous raw materials. Biotechnology can be used to tailor food crops to meet food processing and consumer needs. For example, new plant tissue culture techniques can be used to produce food flavor and coloring ingredients. These methods potentially could replace production and extraction of these ingredients from plants.

Genetic engineering can also be used to alter food characteristics. Genes coding for enzymes involved in starch and lipid biosynthesis are being isolated and cloned, enhancing the prospects of engineering plants with specific compositions of starch and oil. And, genetic engineering is being used to eliminate toxins, allergic compounds, or off-flavor components in plants, and to delay ripening of tomatoes.

New biotechnology products are being developed for food manufacturing and monitoring of animal products for food safety. For example, a genetically engineered version of the enzyme rennet, which is normally extracted from the forestomach of calves, has recently been approved by FDA for use in cheese manufacturing systems. Bacteria and yeast strains engineered to convert waste products such as blood, bone, and milk whey into useful products could decrease the costs associated with their disposal. For example, engineered yeast strains are capable of fermenting the lactose in whey to value-added products, such as vitamin C, biofuels, or pharmaceuticals. Food safety monitoring will be enhanced by the development of nucleic acid probes and monoclinal antibodies; raw materials, ingredients, and finished products can be analyzed for the presence of pathogenic organisms and chemical and biological contaminants. Detection kits are also commercially available for monitoring several pesticides, antibiotics, and bacterial contaminants.

Advanced Computer Technologies

Since the industrial revolution, agricultural systems have intensified, and agricultural productivity has increased significantly along with farm size. Labor-saving devices on farms have increased output per worker several fold, and advances in understanding and application of biological principles have boosted agricultural yields significantly. With increased production, however, farm management becomes correspondingly more challenging and complex. In general, methods for making management decisions have failed to meet this challenge. As a

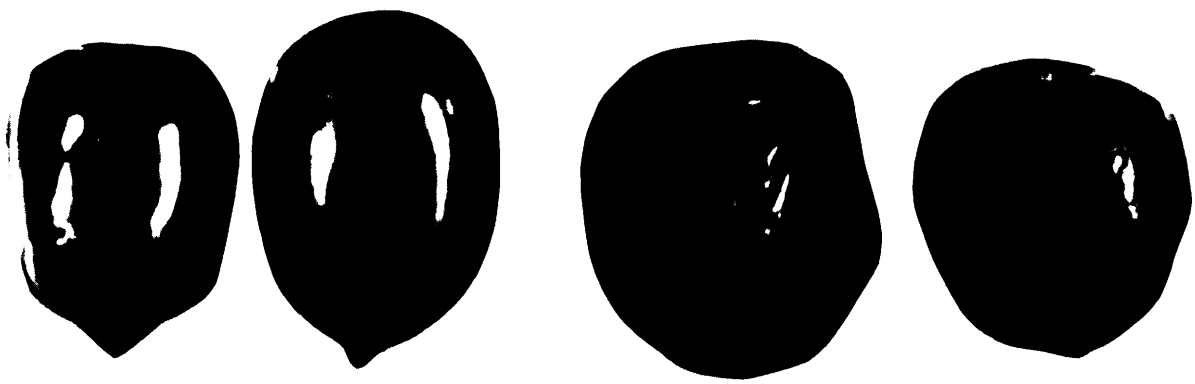


Photo credit: Calgene, Inc

Tomatoes with genes that delay ripening (left) and control (right) 3 weeks after harvest.

result, many decisions are ''uninformed' and many agricultural systems poorly managed.

The application of advanced computer technologies to agricultural management can help remedy this situation. Improved access to information will allow farmers to monitor progress more effectively and to determine suboptimal performance. For example, close monitoring of animal performance will allow early detection of diseases and can help reduce stress in animals.

Overall, advanced computer technologies can provide managers with the ability to systematically determine the best decision rather than arrive at decisions in an ad hoc fashion. Optimal decision making requires a holistic view of a farm enterprise, factors that affect it, and probable consequences of management decisions. Thus, a farmer deciding whether to plant a specific crop on a specific field should weigh the profitability of the crop as well as overall farm needs (e. g., nutrition requirements if it is an animal enterprise). The decision will impact land sustainability and the need to use certain pest-control strategies.

By-and-large, computers have had little impact on production agriculture to date. Predictions that every farmer would own a computer by 1990 have not come true. Few farmers have computers and those that do use them primarily for book keeping and general calculations (e. g., ration balancing).

The largest impact of computers in American agriculture has been in support industries. Using computer networks and tracking systems, equipment dealers can provide faster service, and feed dealers are better able to manage feed inventories. Most of these advances have come from directly adopting general business software with little or no input from the agricultural academic community.

The primary agricultural application of advanced computer technology by the mid - 1990s will be ad hoc expert systems (i.e., computer programs that use knowledge to solve well-defined problems). Problem diagnosis expert systems currently are under development, and farmers will have a cadre of these systems at their disposal to diagnose diseases and to evaluate production performance. These systems generally will not be integrated with one another and each will consider only one aspect of a problem. Integrated systems that solve production problems while considering economic consequences will not become available until the later part of the decade.

The primary use of expert systems within the next 5 years may be by agribusiness which will be able to leverage the cost of adopting these technologies across a number of farms. Using expert systems to increase service to farmers may change the role of some professionals. For example, expert systems can help veterinarians take an epidemiological approach to solving problems. It will also allow some diversification in services provided. For example, animal nutritionists may be more likely to become involved in consulting for the crop program when aided by an expert system.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Farmer and consultant examine data from COMAX (COtton Management eXpert) computer program.

Computer-based sensors will be used on a limited basis to collect real-time data for expert systems. The primary use of sensors will be for monitoring weather and field conditions for crop management. Expert systems will help farmers interpret these data and suggest appropriate management strategies such as irrigation, fertilization, or pesticide treatment.

Another technology likely to see application by the mid- 1990s is full-text retrieval systems. It will be possible for farmers and Extension personnel to have a CD-ROM with all of the latest publications at their fingertips. Using a full-text retrieval system, they will be able to retrieve pertinent information that will help them improve their decisions. For example, when a farm experiences a corn mycotoxin problem, the owner-operator can access an information base to find relevant literature.

Robots for highly specialized, labor-intensive tasks will begin to be applied to agriculture in the late 1990s. This would include robot transplanting of seedlings, pork carcass sectioning, and harvesting of fruits and vegeta-

Photo credit: Gerald Isaacs, University of Florida

An experimental fruit picking robot uses a machine sensor and a computer to locate individual fruit for detachment. Approximately 3 seconds per fruit 'are required.

bles. Robots for milking cows, however, may reach commercial application by the mid-1990s.

IMPACTS OF THE NEW TECHNOLOGIES

The new era of biotechnology and advanced computer technologies will be faster paced than previous technological eras. A more rapid pace of technological change will be fostered by major changes in public policy regarding technology. One of the most important changes was the granting of property rights for new plant varieties, new life forms, and computer software. Patent rights were extended to new plant varieties by the enactment of the Plant Variety Protection Act of 1970. This was followed in 1980 by the U.S. Supreme Court ruling in *Diamond vs. Chakrabarty'* that investors in new microorganisms, whose inventions otherwise met the legal requirements for obtaining a patent, could not be denied a patent solely because the innovation was alive. This decision opened the door to patent a broad range of potential new products of the biotechnology era. Capping this series of policy changes was the amendment to the Copyright Act in 1980 that made explicit provisions for computer programs as (literary) works of authorship.

In previous technological eras most technologies were capital intensive and substituted for labor and land. Many emerging biotechnologies will substitute for conventional purchased inputs. For example, biopesticides will replace some chemical pesticides in plant insect control, biotechnology-improved animal disease vaccines likewise will replace some existing vaccines. On the other hand, some biotechnologies will compliment existing technologies. An example is the genetic transformation of plants to incorporate desired traits. In this case, conventional plant breeding will still be required for incorporation of biotechnology-induced traits into commercial lines, for continued plant improvement selection, and for seed multiplication. In addition, for the foreseeable future, chemical fertilizers will remain important in crop production.

As with past technological eras, successful adoption of specific biotechnology innovations will result in additional profits for some, at least the early adopters. As in the past, increased profits will result mainly from reductions in real production costs per unit of output. This, in turn, can increase productivity and the competitive position of U.S. agriculture.

As with past technological innovation, biotechnology is expected to be supply-increasing in the aggregate. The implications, however, can be quite different for different farms. Late adopters of the new technology, for example, will be faced with lower product prices. This is because early adopters have already reduced their production costs, enjoyed increased profits in their period of initial adoption, and are ready to respond to the next wave of technological innovation. Increased supplies are generally associated with lower prices. Consequently, nonadopters often have higher costs while facing lower prices for their products.

Successful use of technologies of this new era most likely will require changes in the production process and may require a higher quality of management. This may mean increased human as well as monetary capital. Less educated farmers with limited capital resources may find it difficult to implement the new technology successfully. Thus, the new technologies may widen the gap between capital-limited and capital-rich farm operators.

Many advancing technologies are approaching commercialization. In crop agriculture, biotechnology research has advanced at a much faster rate than anticipated just a few years ago, and transgenic crops are currently undergoing field trials. in animal agriculture, vaccines and diagnostics are on the market or will be soon. Growth promotants are going through the regulatory process. Reproduction technologies are advancing at a rapid pace and cloned embryos are currently being marketed. Transgenics are still in the future but considerable strides are being made in the use of livestock to produce high value pharmaceuticals. These technologies and others will impact agriculture in a number of ways.

Table l-l—Estimates of Crop Yield and Animal Production Efficiency by 2000

	Actual 1990	Less new technology 2000	Most likely technology 2000	More new technology 2000
Crops				
Corn—bu/acre	116.2	113.8	128.5	141.6
Cotton-lb/acre	600.0	NA	708.0	NA
Soybeans—bu/acre	32.4	32.6	33.7	36.4
Wheat—bu/acre	34.8	37.7	42.6	53.8
Beef				
Lbs meat/lb feed	0.143	0.146	0.154	0.169
Calves/100 cows	90.0	93.750	96,221	102.455
Dairy				
Lbs milk/lb feed	1.010	1.030	1.050	1.057
Lbs milk/cow/year	14,200.0	17,247.200	19,191.600	20,498.800
Poultry				
Lbs meat/lb feed	0.370	0.373	0.389	*0.428*
Eggs/layer/year	250,0	250.500	258.0	*273.125*
Swine				
Lbs meat/lb feed	0.154	0.174	0.181	0.196
Pigs/sow/year	13.900	14.420	15.750	17.791

NOTE: OTA expresses its appreciatio nto Yao-chi Lu and Phil Coiling, Agriculture Research Service, U.S. Department of Agriculture, for their assistance in deriving the estimates for this table,

NA = Not available.

SOURCE: Office of Technology Assessment, 1992,

Table I-2—Projected Annual Rates of Growth (1990-2000)

	Less new technology	Most likely technology	More new technology
Corn	– 0.210/0	1.000%	1.97%
Cotton	NA	1.66	NA
Soybeans	0.06	0.39	1.16
Wheat	0.80	2.02	4.36
Beef			
Lbs meat/feed	0.21	0.74	1.67
Calves/cow.	0.41	0.67	1.30
Dairy			
Lbs milk/feed	0.20	0.39	0.46
Milk/cow/year.	1.94	3.01	3.67
Poultry			
Lbs meat/feed	0.08	0.51	1.46
Eggs/lay/year.	0.02	0.32	0.89
Swine			
Lbs meat/feed	1.22	1.62	2.41
Pigs/sow/year.	0.37	1.25	2.47

NOTE: OTA expresses its appreciation to Yao-chi Lu and Phil Coiling, Agriculture Research Service, U.S. Department of Agriculture, for their assistance in deriving the estimates for this table.

NA = Not available.

SOURCE: Office of Technology Assessment, 1992.

Production Measures

The advance of agricultural biotechnology will play an important role in increasing agricultural productivity at about the historical rate of the last two decades. (See tables 1- I and 1-2.) The most dramatic increase in animal agriculture is in milk production. Since 1960, the annual rate of growth has been about 2.0 to 2.5 percent. OTA's 1985 projection (24,200 pounds of milk per cow by year 2000) was higher than its current one (19,200 pounds of milk per cow by year 2000). A major reason for this change is the slowness to market of bovine somatotropin. In 1985, bST was predicted to be commercially available in 1987. BST had yet to be approved by the Food and Drug Administration as of early 1992.

Efficiencies in crop production will about match historical trends or climb slightly, and for the most part will exceed OTA's 1985 projections. This, in part, reflects the movement of many of the new technologies from the laboratory to the field at a much quicker pace than thought possible in the mid- 1980s. Even though rates of growth may accelerate during the 1990s, the absolute quantity of yields will, for the most part, be lower than projected in the mid- 1980s. This is due, in part, to the fact that many of the early biotechnology inputs will be substitutes for chemical inputs and, hence, the absolute gain in efficiency will in many cases be negligible. Yields are expected to improve in the latter part of the decade as more is learned about the genetic make up of plants.

Agribusiness, Farm Labor, and Rural Communities

Historically, the commodity-oriented agribusiness sector has been driven by economic forces to produce at

maximum efficiency and to maintain low costs. This has resulted in a system that is effective at converting undifferentiated commodities into low-cost food. Today this sector is undergoing change inspired, in part, by the evolution of more demanding and differentiated food consumers. in response, retailer strategies have emerged that focus on improving service to the consumer. information technology has facilitated the shift of marketing efforts toward the discovery of consumer preferences.

To respond to a more consumer-oriented environment, input suppliers may need to explore how information technology can facilitate the coordination of activities needed to assure particular attributes. Information technologies in the future may facilitate new business strategies by providing improved information flows and by facilitating coordination of production and marketing activities.

To date, input suppliers have experienced more consequences of the new technologies than any other part of the agricultural industry. In anticipation of biotechnology-enhanced seed, chemical and seed input industries have transformed structurally. Multinational chemical and pharmaceutical companies have acquired almost all the major seed companies. Concentration of input industries increases the potential for monopoly power, hence the potential for exploiting farmers in their purchase of improved inputs.

The trend toward vertical integration in agriculture and toward proprietary production processes could result in a captive market for some biotechnology products. For example, a genetically engineered seed might be produced by a large, vertically integrated chemical-seed company with specified inputs such as fertilizer, pesticides, and herbicides produced only by that company. Where product quality is influenced strongly by biotechnologies (i. e., pork by pST); and where highly specialized new markets are formed (i. e., for pharmaceuticals), increased incentives for production-marketing links via contracting and other forms of vertical integration can be expected.

The advancing biotechnology and information technologies generally will shift labor from farming as has been true of past technologies. Newly emerging technologies will displace less farm labor than mechanization, but the farm labor force will have to be substantially more skilled than in the past. For example, a key requirement of the new information technology will be computer literacy. Programs to support skill upgrading of the farm labor force will be needed to capture fully the potential benefits of the new technologies.

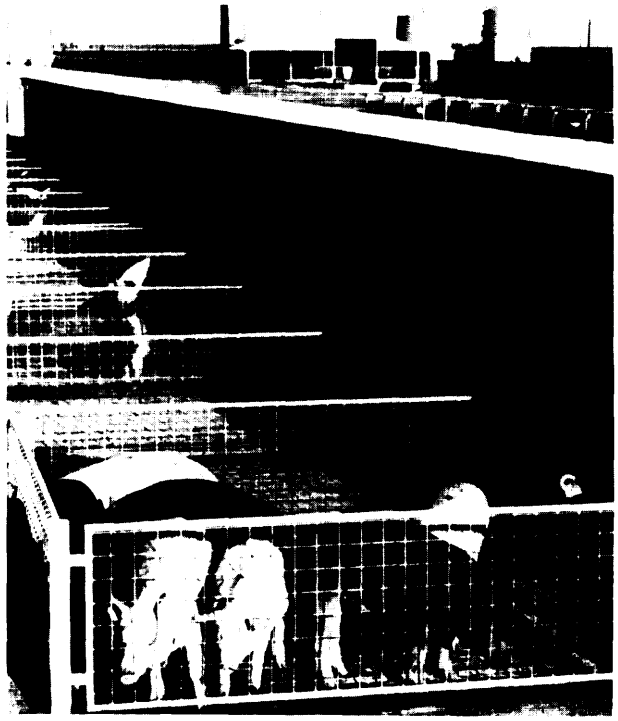


Photo credit: Grant Heilman, Inc.

Production of lean meat with porcine somatotropin (pST) will give meat packers a strong incentive to vertically integrate or contract with farmers. Economic pressures will be strong for most swine producers to adopt pST or exit the industry.

The emergence of biotechnology and computer technologies will most likely spur on the decline of many small farms and agriculturally dependent rural communities. Moreover, increased demand by many farmers for one-stop shopping centers for farm supplies—including those involving biotechnologies and information technologies—may reduce the viability of business enterprises in smaller communities. These enterprises will need to diversify into nonfarm-related economic activities if they are to remain economically viable.

Management

The new technologies will demand greater attention to management issues than have technologies in the past. For crop agriculture, in particular, a systems approach to the use of genetically engineered plants and biocontrol technologies will be needed. Concern about pest resistance to technologies that control pests is reaching a high level. Many chemical technologies are ineffective today because of pest adaptation caused by poor management strategies. As products from biotechnology are used to control pests, management strategies for delaying or pos-

sibly avoiding pest adaptation need to be identified. Evidence exists already that insects are quite capable of adapting to Bt, one of today's most popular genetically engineered protein toxins. At present, there is some information to establish general guidelines about the judicious use of engineered crops with insect and pathogen resistance and herbicide tolerance. However, to establish more detailed guidelines will entail generating a body of empirical knowledge relevant to these products. And, an effective educational program designed to bring these results to the agricultural industry and the public is needed.

For animal agriculture research results clearly show the extent of response achieved from technology depends heavily on the management capability of the producer. Use of somatotropins, for example, may require altering the animals' diets. Administration of somatotropin to lactating cows may require extending the reproductive cycle.

As important as these management issues are, a more pressing issue is that of animal welfare—with or without biotechnology as a complicating factor. Much of the success in increased productivity in agriculture has been the result of lowered costs through the use of confinement systems—which some have coined factory farming. The question from an animal welfare perspective is whether we have gone too far.

The impact of biotechnology on animal well-being is perhaps the most challenging issue genetic engineering raises. The technology is most likely impact neutral in that one could use biotechnology to enhance animal well-being as well as compromise it. Clearly, biotechnology's impact depends on what is done and its effect. If it is used judiciously to benefit humans and animals, with foreseeable risks controlled, and the welfare of animals kept in mind, it is morally defensible and can provide great benefit.

Food Quality

Information about food quality can be provided through labeling, brand names, price, and grades. Food grades are used to classify products according to certain quality characteristics and are established by the U.S. Department of Agriculture (USDA). In particular, they sort a group of foods with heterogeneous characteristics into lots of more uniform characteristics. Biotechnology will challenge the relevance of grades since this new technology is capable of producing products of uniform high quality. For example, as discussed above, pST reduces backfat thickness and increases protein deposition in hogs, resulting in a final product that is more desirable to a health conscious society. Current USDA grading criteria based, in large part, on backfat thickness and degree of marbling will not be relevant since there will be little. if any, difference from animal to animal in these characteristics in products produced with the new technology, For a grading system to be useful, new grading criteria will be needed. What these new criteria should be and how they will be measured are open to question. An argument can be made for providing quality information via labels to consumers and dispensing with USDA grades for most, if not all, agricultural products.

Intellectual Property Rights

Intellectual property protection is one of the most important incentives for the commercial development of biotechnology- and computer-related processes and products. Patents and other forms of intellectual property (plant breeders' rights, trademarks) provide this protection. Patents may be issued in the United States for microorganisms, plants, and nonhuman animals. U.S. patent law is the most inventor-friendly statute in the world: if Congress takes no action regarding patentable subject matter, broad protection for inventions created by biotechnology will continue. The Patent and Trademark Office (PTO) issued its first patent on an animal in 1988. No further patents have been issued since, and the backlog of applications at PTO now numbers at least 160. Since the status of patent applications is, by law, confidential, no way exists to determine when or if the patent office will issue subsequent animal patents; or whether such patents will have agricultural applications. Congress, through its oversight responsibilities, may require PTO to explain the present status of any such patent applications.

Rapid technological advances in computer software is challenging the intellectual property laws in the United States and internationally. Copyright law offers straightforward remedies for the literal copying of program code, although enforcement remains a problem. Functional aspects of computer programs pose difficult questions for application of copyright. The protection of software-related inventions by patent is a fairly recent development and is controversial. PTO faces considerable challenges in examining applications for computer-related inventions. An incomplete data base of "prior art" for computer-related inventions makes it difficult for examiners to judge whether an application describes a "novel" invention. Improving the database of ''prior art' is one important means of improving the quality of the examination but will be difficult because so much of what

constitutes ''prior art' has been in the form of products, not literature or issued patents.

MAJOR FINDINGS AND OPTIONS

For any new technology, it is important to weigh the potential benefits against the risks and possible costs of its widespread adoption. Biotechnology-related risk assessment focuses on the planned introduction of genetically modified organisms into the environment (environmental safety) and on the consumption of products derived from biotechnology (food safety).

In many ways this is a difficult time for a new technology to emerge. Negative experiences with nuclear and chemical industries have made the American public wary of new technologies, and confidence in institutions has eroded. For these reasons, and because the consequences of environmental introductions of genetically modified organisms cannot be predicted with certainty, biotechnology has been subjected to extensive, apprehensive scrutiny and regulatory oversight. Many institutions will choose to "go the extra mile" to ensure public confidence as some policy issues are resolved. In making policy decisions it remains important, nonetheless, to distinguish clearly between the technical basis for assessment and regulation of technology-related risks, and what might or might not be done as an extra step to maintain public confidence. Balancing safety and institutional credibility against economic competitiveness will be a skill much in demand throughout the decade.

Environmental Safety

Findings

Adequacy of a Knowledge Base for Risk Assessment Analysis-After several years of experience with planned introductions, a consensus is growing among scientists that the risks of planned introductions of genetically modified organisms into the environment can, for the most part, be assessed with available analytical capabilities. Although risk assessment is itself a relatively young field, the capacity to identify and weigh risks and benefits in a structured and analytical way has matured rapidly in recent years. Based on experience with other technologically oriented issues such as pollution and its control and food safety, risk assessment as a field has generated principles and methodologies that can be adapted for planned introductions of recombinant-DNA modified organisms in the environment.

The fields of community ecology, population biology, population genetics, evolutionary theory, and agricultural sciences as well as others have contributed to our current understanding of the ecology of planned introductions. Decades of research in life history dynamics, competition, characteristics of colonizing species or disturbed habitats, disease resistance, and gene flow have provided a basis for risk assessment of planned introductions. Thus, while it is impossible to assess the exact consequences of any specific planned introduction, the fact remains that ecological understanding combined with risk assessment methodologies make it possible to analyze the potential risk of each introduction before it is allowed to take place.

Adequacy of a Knowledge Base for Science-Based, Risk-Based Regulations-Reports of the National Research Council, the Ecological Society of America, and the Scope document of the Office of Science and Technology Policy (OSTP) and the Council on Competitiveness all advocate science-based and risk-based regulations of biotechnology applications. The implementation of such regulations draws on the ability of regulators to conduct adequate risk assessments, which in turn rests on the knowledge base and technical capabilities discussed above.

Regulatory oversight rests with Federal agencies, with varying degrees of involvement by state regulatory personnel. USDA's Animal and Plant Health Inspection Service (APHIS) has taken the lead in designing a process for the evaluation of possible risks and benefits when a specific planned introduction of a genetically engineered plant is proposed. Technical information to be provided by an applicant is clearly defined, so that a thorough, science-based risk assessment can be performed. Technical personnel in fields such as genetics and ecology have joined the staff of APHIS's Biotechnology, Biologics, and Environment Program (BBEP), to ensure vigorous assessments. State regulatory personnel are drawn into the process so that they can provide additional technical information specific to local habitats and add an additional perspective.

The Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP) has extended its review processes under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA) to planned introductions of microbial pesticides; it also cooperates with USDA-APHIS in reviewing proposals for introduction of pest-resistant plants. EPA's Office of Toxic Substances (OTS) has recently published draft regulations to cover planned introductions of genetically modified microorganisms; significant controversy exists as to whether these regulations are indeed science- and risk-based, or whether they sim-

ply single out biotechnology for attention because it is biotechnology. The final status of these regulations, as well as their implementation processes, is not yet known. State agencies have yet to be pulled into EPA regulatory processes to the extent accomplished by USDA.

Extent That Regulations Are Product-Based—Re- ports of the National Research Council and the Ecological Society of America stated that the techniques of biotechnology are not themselves inherently risky or unmanageable. In line with these findings, the early Coordinated Framework, the document that established responsibilities of Federal agencies that regulate biotechnology derived products, and the principles put forth by OSTP and the Council on Competitiveness recommend that biotechnology not be regulated as a process. Rather, a central tenet for biotechnology regulation is that the various products of biotechnology should be regulated, just as are products of other technologies.

The product/process distinction has generated a great deal of controversy in the past. However, as the experience base with biotechnology has grown, the premise of judging each product on its own basis rather than automatically implementing special regulations, has gained wide acceptance. The extent to which this premise has been implemented, however, varies among agencies.

Though its focus is on plant pests, USDA-APHIS has been able to include along with other organisms under its purview any vector, vector agent, donor organism, recipient organism, or any other organism or product produced through genetic engineering if it can be defined as a pest. This product-selective approach makes it possible for regulated articles to become exempted from special review as evidence indicates their safety.

Under FIFRA, EPA-OPP also has applied an existing mandate to products of biotechnology, specifically plants engineered to produce compounds aiding them in resisting pests. By pulling these ‘‘pesticidal plants’ under the rubric of its oversight for pesticides, EPA-OPP seems in one sense to be focusing on the product rather than the process by which it was generated. However, a question exists as to whether or not *‘pesticides’ is the appropriate category into which to place these particular products, especially since naturally occurring plants produce some anti-insect compounds (see next section). To assume authority over plants genetically modified to be resistant to pests, EPA-OPP seems to have chosen to look only at plants that have gone through a biotechnology process, leaving naturally-occurring pest-resistant plants alone.

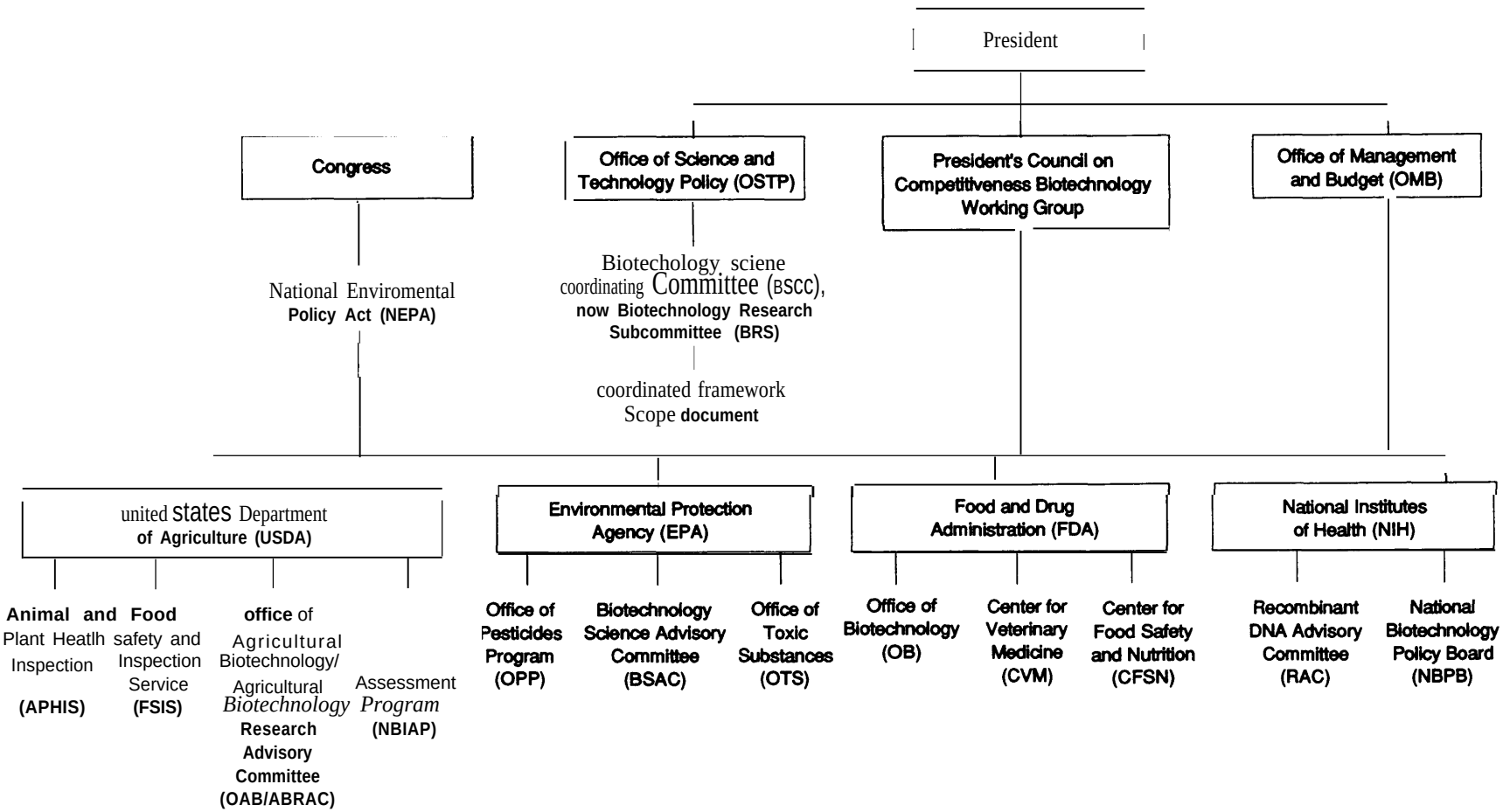
Under the Toxic Substances Control Act (TSCA), EPA-OTS has promulgated draft regulations for oversight of microorganisms that do not fall under other authority. However, under these draft regulations, essentially all microorganisms other than those modified through biotechnology techniques are automatically exempted from review, whereas those modified through biotechnology techniques are labeled “new” and therefore subject to regulation. When the only products subjected to special review are biotechnology products, a question arises as to whether or not the regulations are contradicting the scope principles by focusing on process. The draft regulations under TSCA have been charged by some with automatically and unfairly assigning a special riskiness to organisms modified through biotechnology, while exempting organisms that are known to be potentially dangerous but not produced through a biotechnology process. This discrepancy, and perhaps its final resolution, underscores a central tenet of regulation—that regulation should be based on scientifically determined risk.

Appropriate Review Authority for Plants Genetically Modified for Pest Resistance—Under the Coordinated Framework (figure l-l), which established the responsibilities of Federal agencies with regard to biotechnology, EPA-OPP took on authority for plants into which genes coding for compounds toxic to insects had been introduced. The premise was that these were special “pesticidal plants” that presented risks to the environment, food, and human health similar to traditional chemical pesticides applied externally in large volumes to plants.

This premise is questioned for several reasons. Compounds toxic to insects that are part of plant tissue do not cause pesticide run-off and other such environmental problems (so long as they are alive); they are distinctly localized. Furthermore, most of the compounds are not complex, like many synthetic compounds, and may well be more readily biodegradable.

Another key argument with the premise of singling out plants genetically modified for enhanced resistance to pests is that all plants have natural pest resistance characteristics. Selection pressures over evolutionary time have favored the spread of genes in natural populations that code for characteristics unattractive or harmful to insects. Making a distinction between genetically modified plants and natural plants that are pest resistant, calling the former ‘‘pesticidal plants’ and the latter simply ‘‘plants’ is in fact arbitrary, not science-based. If the “pesticidal plant” premise is disallowed, an argument then exists that EPA-OPP is not automatically the best home for regulatory review of such plants.

Figure I-1—Jurisdiction and Coordination of Environmental Policy for Biotechnology-Derived Agricultural Products.[a]



USDA statutes
- **Plant Pest Act**
- **Plant Quarantine Act**
- **Noxious Weed Act**
- **Virus-Serum-Toxin Act**
- **Federal Meat Inspection Ad**
- **Poultry Products Inspection Act**

EPA statues
- **Federal Insecticide,** Fungicide, **and Rodenticide Act (FIFRA)**
- **Toxic Substances Control Act (TSCA)**

FDA statues
- **Food, Drug, and Cosmetic Act (FDCA)**

[a]OSTP, the Council on Competitiveness, and OMB do not have direct oversight over the Federal agencies; the connections shown here are those of influence through law, key policy documents, or review.

SOURCE: Office of Technology Assessment,1992.

Finally, EPA-OPP has in the past dealt with chemicals and, to a small but growing extent, microorganisms. These are the areas of staff expertise, for the most part, not plant ecology. The latter is the strength of USDA-APHIS. In fact, USDA-APHIS currently takes the lead in assessing applications for field trials of plants genetically modified for enhanced pest resistance. In consultation with EPA-OPP personnel, USDA plant scientists employ their plant expertise and their established review system toward this end. Although companies and universities have moved ahead and conducted tests, the unclarified status of OPP's approach to large-scale commercialization worries these parties as well as State governments. Treating all crop plants as pesticides would take an immense toll in State government time and personnel; yet States cannot plan because they have not as yet received guidance from EPA as to what is coming.

Appropriateness of TSCA for Biological Commercialization- Can or should a law written for chemicals, specifically TSCA, be used to cover living organisms'? Essentially, this is happening as the traditional role of "gap filler" played by TSCA is applied to planned introductions of microorganisms used for purposes other than as pesticides. Approval for the introduction of microorganisms rests on determination that they will not harm human health or the environment. Microorganisms themselves are not toxic; neither are they likely to be applied in the volumes typical of chemical applications. Instead of persisting as do many synthetic chemical compounds, living organisms are eminently biodegradable. However, because they can potentially reproduce themselves and spread in the environment, their use brings up concerns different from those aroused by chemicals.

TSCA could be stretched to cover microorganisms. However, biologically trained staff will have to be given the authority to develop the procedures and requirements of the office. Managers will have to acknowledge the differences between microorganisms and chemicals, and back up their biologically trained staff accordingly, when different treatments are devised. Paradigmatic shifts in management policy need to occur if EPA is appropriately to adapt to living organisms those laws, premises, and procedures originally designed for chemicals. EPA's ability to evidence such flexibility is questioned.

Managing Risks of Large-Scale Introductions—As agricultural biotechnology moves toward commercialization and large-scale planned introductions, the combination of several approaches can maximize benefits and minimize risk. Technically sound implementation of science-based regulations are critical to risk management, as are technically competent regulatory personnel. In addition, specific scientific and agronomic methods are needed to manage risks of particular planned introductions. Examples are methods to reduce the chances for horizontal gene transfer or to diminish the survival potential of any non target recipient of an introduced gene. Scientists are exploring ways in which the gene of interest, or supplementary genes transferred along with it, can be designed to constrain the potential for transfer (a kind of internal, genetic "containment" system).

Agronomic methods can also be used to manage identified risks. For example, physical or spatial barriers could be put in place between a field of genetically modified crop plants and the adjacent field or surrounding natural vegetation. While this sort of barrier would probably not be necessary in most cases, in particular cases where gene flow was of concern (perhaps for canola), this could be useful. Other mechanisms could be used as well, such as surrounding a field of genetically modified plants with barriers of a "trapping" species that attracts any pollinators that might otherwise carry genes from one of the modified crop plants to other plants. The actual need for such ''separations'—whether spatial, or temporal—can be determined by assessing the risk of gene flow or of establishment of genetically modified organisms.

Photo credit: Grant Heilman, Inc.

A traditional approach to isolation **of** plants is to spatially separate desired plants from other plants. Similar guidelines for spatial separation have been applied to transgenic plants as well.

Risks of Genetically Modified Plants or Microorganisms Becoming Pests—Any novel organism potentially represents some level of risk to the environment, whether that organism is naturally occurring or genetically modified. However, the likelihood of a genetically modified plant or microorganism actually becoming a pest is relatively low. The long history of agriculture shows that current crops are not likely to become established as weeds. Long established mechanisms for containment in agricultural systems have been highly successful in the United States. Furthermore, recombinant-DNA modified organisms, unlike wild, naturally occurring organisms, are designed to exist only in a specific environmental regime—the nurturing surroundings of a cultivated field.

Microorganisms modified for agricultural purposes are constrained somewhat like plants, although they are not so dependent on cultivation for continued survival. However, the extensive agricultural experience with microorganisms has not resulted in a pest problem. To become a pest, an agricultural plant or microorganism has to exist independently of cultivation—outside the planted field. Several steps are necessary to its success; each one, from dispersal to the production of viable, competitive offspring, is not likely to occur.

Potential for Gene Transfer or Cross-Hybridization Between Genetically Modified Plants and Wild Plants-Cross-hybridization, the crossing of two plants of different species to produce fertile offspring, is a rare phenomenon. While gene transfer between individuals of the same species is straightforward, gene transfer between different species is not; their genetic compositions are usually sufficiently different that they do not line up and match well for the key molecular and cellular events of reproduction. Even if a transferred gene were involved in such a cross, it would be cast onto an ‘‘alien’ genetic background—its expression could be problematic.

Most crop species in the United States do not have indigenous weedy relatives with which they could cross-hybridize. Canola is the only major crop for which related weedy species exist in the United States. The possibility of cross-hybridization is greater in other countries, where crop species and related weedy species do coexist. Developing countries, in particular are the centers of origin for many crop species. As it exports agricultural biotechnology capabilities, the United States has at least a moral responsibility to provide advice to developing countries as to the management of risk from cross-hybridization.

Options

1. The tools of biotechnology offer great potential to American agriculture; regulatory treatment of agricultural products derived with such tools will play a dominant role in any related gains or losses in economic competitiveness. Science-and risk-based regulation of products can help ensure safety while not impeding the economy.

. *Congress could directFederal regulatory agencies to make science-based, risk-based regulation of biotechnology products (not process) a unifying policy across agencies.*

This would be a clear message to the executive branch that Congress expects a unified approach across Federal agencies based on the product not on the process of biotechnology. Communication through interagency groups would help to ensure a common approach based on scientifically determined product risk. This approach can help protect health and environment and, at the same time, should generate a comprehensive, workable regulatory apparatus for incorporating the tools of biotechnology into American agriculture. However, EPA will need to address their shortage of technical staff needed to conduct technical risk-based reviews.

No scientific evidence exists to justify Congress directing agencies to review and regulate biotechnology as a process, rather than the products produced by it. Nevertheless, EPA-OTS has been accused of regulating the process of biotechnology, not the products, in its proposed rules. If agencies were to ignore the use of risk assessment of products and automatically penalize any efforts made using biotechnology, several impacts would likely occur. Industries and universities probably would ‘‘agency -shop,’ orienting their efforts toward the agency with the clearest analytical assessment of science-based risks—that agency will be the least arbitrary and the most predictable, an approach certainly favored by industry. The agency regulating biotechnology as a process sends out an obvious negative message to industry and perhaps an equally important, if more subtle, message to the public. Regulations based on the assumption that biotechnology is inherently unpredictable and highly risky can lead to reverse public reactions and political pressures that may be detrimental to the economic competitiveness of American agriculture.

2. **Enhanced pest resistance in crops is one of the most promising applications of new biotechnology tools. Obstacles to its development could send a negative message to agribusiness, slowing its incorporation of**

biotechnology as a mechanism fostering increased economic competitiveness.

. *Congress could keep the oversight authority for plants genetically modified, for enhanced pest resistance under EPA Office of Pesticide Programs (OPP), but direct EPA to strengthen OPP.*

If oversight of "pesticidal plants" introduced at a large-scale is to be handled effectively by OPP. several changes would need to occur. Technical staff with plant expertise would need to augment current staff; definitions would have to be clarified, given that some naturally occurring plants contain more "pesticidal compounds'" than will the products of biotechnology: communication with State-level implementors would need to be improved immediately; and a clear approach would have to be articulated so that the public, industry and academia would know where the agency stands and how it will implement its policy.

. *Congress could direct USDA-APHIS to regulate large-scale introducation of plants genetically modified for enhanced pest resistance.*

Since USDA-APHIS-BBEP has taken the lead for field tests of plants genetically modified for enhanced pest resistance, APHIS could handle large-scale introductions. This has the advantages of centralizing plant oversight and making effective use of an already well functioning technical staff and organizational unit. The chief disadvantage would be a disruption in the original Coordinated Framework, which ascribed authority to EPA-OPP.

. *Congress could direct EPA to work with USDA to develop a similar model of operation and to report on progress to Congress within a specified period of time (e.g. ,* 6 *months).*

Despite disadvantages of 'forcing' two very different offices to work closely together, this has the advantage of allowing USDA to handle any risk concerns related to planned introductions, while allowing EPA to continue to handle food-safety concerns related to ''pesticidal' toxins in the food supply. USDA has established a strong track record for taking the lead in field tests of pest-resistant plants.

3. **TSCA is a statute explicitly designed to regulate activity "for commercial purposes. " Academic research, therefore, has been exempt from TSCA oversight. The proposed draft rules for microorganisms, however, greatly expand the regulatory "net." One rationale for including academic research is that sometimes universities engage in technology transfer or patent filing, or receive research funds from companies. Obviously, the effects of microorganisms being placed in the environment by a university scientist are no different from the effects of those same microorganisms being placed in the environment by an industry scientist. Concern exists, however, that the draft rules could have a negative impact on academic research.**

● *Congress could allow the proposed ru1e to stand, placing the same requirements on academic research as on industrial research.*

Subjecting universities to the requirements placed upon companies seems contrary to the Congressional intent behind TSCA. It could have significant negative impacts on university research. Faced with the added bureaucracy and high costs entailed by this rule, the majority of university researchers might deliberately avoid planned introductions of genetically modified organisms. This would leave industry in charge of an area of research that could continue to benefit from broad, objective, openly published study. Such a situation would inhibit the production of new knowledge for use in future risk assessments. However, it is an arbitrary decision to exclude universities automatically from oversight—the release of organisms that pose a risk should be regulated regardless of who conducts the release.

. *Congress could direct EPA to develope an oversight mechanism for planned introductions as an alternative to the proposed TSCA rule.*

Universities could make use of their already existing system of oversight committees and institutional biosafety officers to regulate biotechnology field trials ''in house'. Just as the Institutional Biosafety Committees *(IBCS) review* laboratory research involving recombinant DNA, they could review proposals for planned introductions. It would entail education of laboratory-oriented personnel as to the ecological considerations of field release, as well as possible expansion of committee membership to include appropriate disciplines. Serving on an IBC is a time-consuming effort for university personnel. Many feel that there are already too many university committees on which they must serve. Use of IBCS to provide oversight is a possible trade-off for the university between being able to conduct this research or not.

. Congress could *direct EPA-OTS to develop special procedures to minimize or eliminate any unwarranted regulatory burden on universities, to ensure that public research continues in this area, and to report to Congress on the method selected and its results.*

This option would still hold public scientists accountable but would be aimed at lessening the regulatory burden if the appropriate procedure is used. Several possible procedures exist. One possibility would be that the agency funding the research would have the responsibility for monitoring and reviewing the work. As part of the funding contract, the principal investigator would agree to follow EPA guidelines on management and to contact EPA if the need arose. This makes it possible for the funding agency to monitor the project and enforce regulations through the distribution of funds.

Another approach is to streamline the application for public researchers. For example, an abstract of a grant proposal could be required to contain specific information that would be sufficient to trigger important questions that arise about the project from EPA. Another possibility would be for EPA to set aside a budget for reimbursement of costs incurred in filing an application. However, even if a cost-savings mechanism is developed, a bureaucracy-minimizing mechanism will also be necessary if Congress desires to encourage public researchers and their home institutions to conduct the objective research that will contribute further to our knowledge base.

, Congress *could amend TSCA to exclude universities or to provide alternative means to regulate academic research.*

An argument can be made for including academic researchers. Obviously, genetically modified organisms released into the environment by a public researcher have the same effect as the same organism placed into the environment by an industry scientist. On the other hand, concern exists about the legal precedent that could be set by extending TSCA's scope to noncommercial research and that it could have a negative impact on research. An application fee for a single field trial costs between $180,000 and $600,000. Even the lower cost is more than most universities or research grants are able to cover. Even though companies have personnel and a budget to cope with regulatory processes, universities for the most part do not have regulatory policy offices or the budget for filing applications. However, if universities and industry worked together, industry would benefit by not having universities file applications. Congress could make its intent for universities clear by stating it in legislative language through TSCA.

4. **As large-scale planned introductions become imminent, companies are looking to the regulatory agencies for guidance as to how to proceed. Clear guidance is critical to commercial development of agricultural biotechnology.**

. *Congress could direct EPA-OPP and OTS to clarify their regulatory approaches to large-scale introductions and report back to Congress on their approaches within u specified period of time.*

Interagency work groups, as well as the leadership of EPA, can orient efforts toward assisting EPA staff in clarifying the regulatory guidelines. A flexible approach seems appropriate. Clarifying regulatory guidelines would be particularly helpful to agribusiness working with "pesticidal plants" or microorganisms other than microbial pesticides. USDA-APHIS-BBEP could provide model mechanisms for clear communication of requirements, use of input from outside the agency, addition of technologically-trained personnel, and creation of an effective structure as well as clarification of direction.

. Congress could *direct EPA to continue on its present course.*

This is basically a status quo option. It would mean a continuation of the lack of clarity of regulatory policy for potential applicants at the large-scale stage. This lack of predictability could have a negative impact on industry. The absence of applications to EPA-OTS for environmental releases under TSCA over the last year illustrates industries' response to lack of predictability in the regulatory arena. It also undermines public confidence in the ability of regulatory agencies to regulate biotechnology.

. Congress could *conduct over-sight hearings of EPA and USDA regarding regulatory policy for large-scale release.*

Oversight hearings could assist the agencies to develop policy to meet congressional intent for regulating these products even though the regulatory agencies have stated that current laws are sufficient for regulation of products derived from biotechnology. This could help clarify differences in laws written primarily for chemicals instead of genetically modified organisms.

5. **Institutions handling new technology must win public confidence and be responsive to public concerns. A balance between maintaining the public interest and ensuring industry competitiveness must be achieved.**

. Congress could *direct EPA and USDA to emphasize: 1) increased input of public participation into their* Systems; 2) *an open process;* 3) *scientifically sound procedures communicated clearly to other scientists; and 4) follow-up on appropriate cases.*

Most systems can be made sounder when external input is factored into decisions. External advisory committees, hearings, and informal workshops are examples of mechanisms by which Federal agencies can obtain such input. EPA-OPP for example, cosponsored workshops on transgenic plants to gain scientific advice as they deliberated their approach to "pesticidal plants" and has used its scientific advisory board in deliberations over TSCA draft rules. USDA-APHIS has held a variety of conferences and workshops on planned introductions, stressing public input and State officials' input. In fact, USDA-APHIS has made State input an integral part of its review process; EPA could wisely adopt this approach in OPP and OTS.

By developing scientifically sound procedures for determining data needs and communicating them clearly, an agency can build an accessible database and contribute to and benefit from the input of the scientific community. USDA's Agricultural Research Service is complementing the work of APHIS by building a database on field tests.

Parties concerned about a new technology want to know that potentially problematic cases are being subjected to close follow up. While USDA and EPA can and do impose monitoring requirements on field tests, both agencies could benefit from implementing more extensive follow upon specific cases that might prove troublesome (perhaps by monitoring indicators identified for a Possible worst-case scenario). This is, of course, time consuming. However, if implemented, it should be used in a rigorous manner, so that undue burdens are not placed on straightforward cases, yet so the public feels secure in the knowledge that problematic cases will be tracked after introduction.

. Congress could require regulatory agencies to develop explicit plans for building public confidence and report those plans to Congress.

This option would give agencies maximum flexibility. It would allow for the evolution of regulation based on the experience of the agency. Moreover, this approach would allow for a solution to be developed within the agency as opposed to it being imposed on the agency from outside. Reporting the plan to Congress would allow the public to express its opinion and to exert pressure on the agency to change those parts of the plan found to be unacceptable. On the other hand, this process is time consuming for the agencies and Congress. With the large demands on Congress, some members probably would be concerned that it was not the best use of their time.

. If regulatory agencies fail to maintain public confidence, new Law(s) or congressional oversight could be established to satisfy the public demand for account ability.

This option is relatively drastic and could have several disadvantages. Managing a system from the outside invites logistical and other difficulties. Moreover, the tendency with this approach would be to "freeze" procedures at a particular moment. This could hamstring the natural and positive evolution of regulation, such as the gradual extraction of generic principles from case-by-case reviews. More generally, this approach would be more in the nature of imposed management rather than a solution developed within the agencies, and as such, its own credibility may be weakened. However, it is an option that could ensure accountability to the public if regulatory agencies are incapable of doing so themselves.

Food Safety

Biotechnology is not so different from previous agricultural technologies as to raise novel scientific issues concerning the safety of foods. What is substantially different, however, is the climate in which this new class of technologies is being introduced. Society in general is more skeptical of the need for new technologies. Scientific illiteracy combined with a lack of knowledge about agriculture and biology leads some people to misunderstand how and why these technologies will be used. Society is also skeptical of how new technologies are developed and regulated. Scandals involving institutions that develop and regulate these technologies have shaken the public's confidence in the ability of these institutions to carry out their activities responsibly. Public confidence will sink further if the public feels that food safety standards are too lax, are fraught with scientific uncertainty, or are not adequately enforced.

In addition, uncertainty exists within industries as to how new food technologies will be regulated (table 1-3). FDA policy has been a long time in the making for biotechnology-derived products. EPA has yet to establish guidelines on data requirements to establish residue tolerances for pesticidal plants, and USDA's Food Safety and Inspection Service (FSIS) has not established guidelines concerning transgenic animals. Genetically engineered products, plants in particular, are approaching commercialization at a faster rate than was anticipated even 5 years ago. These agencies no longer have the luxury of long time frames in which to articulate policy.

An end to the uncertainty over how these products will be regulated is needed. Additionally, general need exists

Table 1-3—Federal Agencies Primarily Responsible for Food Safety

Agency	Principal statutory authority	Responsibilities
Food and Drug Administration	Federal Food, Drug, and Cosmetic Act	Safety/quality/effectiveness of animal feeds and drugs, and all foods except meat and poultry
USDA-Food Safety and Inspection Service	Federal Meat Inspection Act and the Federal Poultry Products Inspection Act	Safety/wholesomeness/accurate labeling of meat and poultry products
USDA-Agricultural Marketing Service	Egg Products Inspection Act	Safety/quality of egg products and shell eggs
Environmental Protection Agency	Federal Insecticide, Fungicide, Rodenticide Act	Safety of pesticide products
	Federal Food, Drug, and Cosmetic Act	Pesticide residue tolerance in food/feeds
National Marine Fisheries Service and Food and Drug Administration	Agricultural Marketing Act	Voluntary seafood inspection

SOURCE: Office of Technology Assessment, 1992.

to regain public confidence in the regulatory agencies responsible for determining the safety of new biotechnology products.

Findings

Establishment of Federal Regulations and Guidelines Concerning Biotechnology FoodProducts—in the first half of the 1980s, it was anticipated that animal biotechnologies would be developed more quickly than plant biotechnologies because more was known about animal physiology than plant physiology. However, several scientific breakthroughs have speeded progress toward transgenic plants and some are now in various stages of field testing. As transgenic plants approach commercialization, scientific guidelines for assessing their safety will be needed. Further delay in establishing Federal regulations and guidelines could cause a competitive disadvantage to industry, as well as continue to undermine public confidence in the ability of regulatory agencies to establish a clear policy concerning biotechnology.

FDA is now wrestling with the question of whether to classify all, none, or some transgenic plants as food additives and to require a food additive petition for these foods. In May 1992, FDA published a preliminary proposal regarding the regulation of new varieties of genetically modified crops. This policy states that FDA is concerned with the characteristics of the food product and not with the method used to produce the product. Thus, new genetically modified crop varieties will not automatically be required to obtain a food additive regulation. New varieties that do not contain new toxicants, elevated levels of inherent toxicants, altered nutrient composition or bioavailability, or enhanced allergenic potential may be regarded as not significantly different from conventionally produced new varieties that are generally regarded as safe. These varieties could be marketed without premarket oversight by FDA. The adulteration clauses of the Federal Food, Drug, and Cosmetic Act could be used to remove these varieties from the market if FDA disagrees with a firm's safety evaluation. Varieties that contain substances (either gene expression products or unintended products) that differ significantly in structure, function, and composition from substances currently contained in foods may be required to obtain a food additive regulation.

The lack of a priori oversight of some new varieties, however, may still leave considerable uncertainties in the minds of the public, at least for the first generation of products developed. Public confidence in the process may still require at least a minimum review of the product prior to commercial release. Such review may consist of notifying FDA of the development of a transgenic crop and provision of a minimum level of data so that FDA can make a determination as to whether a food additive petition will be needed. Such a notification process could be open to the public so that any significant concerns can be identified. Additionally, public interest groups have expressed opposition to the policy and have threatened legal action to prevent its implementation. The policy is currently open to public comment, and could be subject to revision. Congress may yet be required to intervene in the development of food biotechnology regulations if differences cannot be resolved in a timely fashion. If such action is needed, several options are available to Congress.

Public Confidence in the Decision making Process— One method of enhancing public confidence in the regulatory process is to make that process open and accessible and to increase public participation in the process. Opponents of increased public input in regulatory decisionmaking processes argue that citizens lack the training needed to understand complicated scientific and technical

issues, and as such their participation only delays the agency's decisionmaking without offering any offsetting benefits. Critics also fear that public representatives may act in emotional and irrational ways and make unreasonable demands. Those who support increased public input argue that such input is invaluable in establishing the legitimacy of regulatory decisions. Indications also exist that public participation can increase the comprehensiveness of agency decisions by encouraging the agencies to focus on a wider range of issues and values than they normally would. Lastly, it is hard to justify no public participation in regulatory processes in a democratic society.

The public will not make the regulatory decisions—that is the responsibility of the State and Federal agencies whose statutory authority requires them to ensure a safe and wholesome food supply. However, public confidence that these agencies are fulfilling their responsibilities will be enhanced if there are mechanisms available for public questions and concerns to be heard and addressed prior to decisionmaking by the regulatory agency. At present, public input into the regulatory process consists of notification and comment procedures and participation on advisory committees.

Recent revelations that companies have withheld negative research results from regulating agencies have also undermined public confidence and raised serious questions about the process used in making safety assessments. Currently, manufacturers of technology submitted to the regulating agency for approval also perform the safety assessment following guidelines established by the agency. This situation creates potential conflicts of interest. Most companies are honest, but given the current climate of public skepticism, the appearance of impropriety may be sufficient to prevent consumer acceptance of a new technology. Given the lack of public understanding about biotechnology, doubts about the validity of the safety data used to make regulatory decisions for this new class of products could be substantial. There may be merit in considering a safety assessment process that includes independent testing of products.

Tradeoffs Between Industry Competitiveness and Society's Right to be Informed About Health and Safety issues—Public interest groups argue that industry claims too much scientific data as confidential business information (CBI) when submitting a new technology for agency approval, thereby limiting the amount of health and safety data available to the public. On the other hand, industry feels that there is too little protection of proprietary data by Federal regulatory agencies. Achieving the proper balance between protecting proprietary rights and disclosing health and safety data to the public is a delicate undertaking.

Disclosure practices are regulated by the Trade Secrets Act and the Freedom of Information Act. The Trade Secrets Act of 1982 subjects government employees to criminal penalties for the disclosure of proprietary data unless authorized by law. The Freedom of Information Act (FOIA) of 1982 permits agencies to protect trade secrets and commercial and financial information that is confidential. Both laws seek to protect information that would be of commercial value to a firm's competitor. However, a congressional order mandates that EPA and FDA release some types of scientific data in certain circumstances.

The FDA has restrictive CBI policies. Although Congress has mandated that health and safety testing data for new drugs can be released after another manufacturer becomes eligible to sell the drug unless extraordinary circumstances are shown, little data are actually released. This is in part because FDA defines extraordinary circumstances to include any claim that the data are CBI, such as a claim that it could be used by competitors in foreign countries.

While FDA usually does not release safety data, it did in the case of bovine somatotropin (bST). For the first time in FDA history, FDA published an article in a peer reviewed scientific journal detailing how FDA reached its conclusion that bST was safe for human consumption. Specific safety data were presented. Additionally, the National Institutes of Health (NIH) and FDA hosted a scientific meeting with public participation to discuss food safety concerns of bST. FDA has also published an article explaining why FDA granted GRAS status to the genetically engineered enzyme chymosin. Thus, FDA has shown that it is possible to release such information when it is in the public interest.

FIFRA protects CBI, but allows release of health and safety testing data for registered pesticides. Also, data concerning production, distribution, sale, or inventories of a pesticide maybe released in connection with a public proceeding if disclosure is in the public interest. Thus, FIFRA permits the release of health and safety data after the decision is made but not during the process.

After notification of a food additive or pesticide registration petition has been published, under FOIA, requests for safety data can be made. However, sometimes it is not possible for agencies to determine whether or not information is CBI in the time allotted to them to make a regulatory decision. Attempts to mitigate these

problems include requesting that companies restrict their CBI claims and that they justify their claims of confidentiality at the time they submit a petition.

Decisions to disclose CBI focus on whether or not such disclosure will be harmful to the company. No attempt is made to weigh this harm against the public's right to be informed about health and safety issues that might affect them. Other countries, most notably Canada, have taken the approach that disclosure of health data is authorized if it is in the public interest as it relates to public health, public safety, or protection of the environment and if it clearly outweighs in importance the financial loss to the competitive position of a company or person.

Enforcement of Regulations-Research indicates that a significant factor in public lack of confidence in regulatory agencies is concern that regulations are not adequately enforced. For example, although Federal law bars sale of produce with pesticide residues above Federal tolerances, recent studies show that consumers are willing to pay for labels assuring them that these tolerances are in fact not exceeded. If the public is to regain trust in regulatory agencies, enforcement of regulations will need to be improved.

This will be difficult as biotechnology becomes a new focus of public concern and a new arena of regulatory responsibility. The regulatory agencies do not have the resources to increase enforcement activities significantly. A recent General Accounting Office study found that the regulatory agencies involved in food safety had fewer staff, less funding and a larger workload in 1989 than in 1980. Available resources already are being stretched, and must be spread even thinner to develop new multiresidue assay procedures and sampling methodologies for tracking genetically modified organisms. A new approach to food safety assessment must be developed as well. Traditional approaches to safety assessments of food additives are inappropriate for the assessment of whole foods because large enough quantities of the food cannot be fed to test animals without invalidating the results of the test. New assay and testing methods applicable to genetically modified foods will thus be needed, and this will require additional agency resources.

Labeling—Many consumers have expressed a desire that food products developed with biotechnology be so labeled. However, while consumers express a desire to have accurate and verifiable labels, many of them are not willing to pay much for those labels. For example, approximately one-third of consumers do not seem willing to pay anything for labels; another 5 to 10 percent of consumers seem willing to pay as much as 50 percent higher food prices for labels. Most consumers seem willing to pay 5 to 10 percent more for labels. Clearly a labeling proposal that is expensive will not be popular with most consumers.

Photo Credit: U.S. Department of Agriculture, *Agricultural Research Service*

Chemist evaluates a screening assay for residues. New analytical methodology will need to be developed for biotechnology-derived foods.

FDA has stated in its preliminary policy that generic labeling of biotechnology food products will not be required but selected products may require labeling. Such products include those for which nutritional composition has been altered or potential allergens introduced.

International Coordination—The United States annually imports billions of dollars worth of food products, many from countries that also use biotechnology in their food industries. If U.S. food safety regulations concerning biotechnology substantially differ from other countries' regulations, difficulties could arise. U.S. producers will likely beat a competitive disadvantage if U.S. policy

is substantially stricter than that of other countries. Enforcement will be difficult—no generic methods exist to detect genetic modification. Reliance on the word of other countries that their products contain no biotechnology-derived constituents may or may not be acceptable. If U.S. regulations are substantially less stringent than those of other countries, then the U.S. agricultural export market could suffer. Agricultural commodities are a major export of the United States. Thus, international coordination will be paramount. Preliminary FDA policy is consistent with international organizations' working papers and reports on food safety assessment procedures for genetically modified organisms.

Options

1. FDA and EPA no longer can delay the development of final regulations and guidelines because transgenic plants are approaching commercialization. FDA **has the choice of requiring a food additive petition for all, some, or no transgenic plants.**

. *Congress could monitor the development of regulations and conduct oversight hearings of FDA and EPA to determine why final regulations and guidelines do not exist and to have them report back to Congress with recommendations in these areas within a specfied period of time.*

This would be a strong signal to the executive branch that Congress is concerned about the delay in providing guidance to the private sector for these new technologies. An oversight hearing would provide the agencies with an opportunity to explain their rationale and concerns in establishing regulations for these new products and allow Congress the opportunity to provide guidance and direction to the agencies.

Congress and the Executive Branch through EPA, FDA, and USDA have a number of options for regulating transgenic organisms. The following part of Section 1 illustrates options available.

. *Congress or FDA could establish categorical exclusions to the requirement of a food additive regulation for certain transgenic organisms and require a case-by-case approach for the remaining products.*

Essentially, this is the policy chosen by FDA. Transgenic organisms that involve gene products that are widely present in the current food supply, and do not introduce new toxicants, elevate levels of existing toxicants, alter the composition or bioavailability of nutrients, or transfer allergenic components, and that use safe marker and promoter sequences can be excluded from the need for a food additive regulation. These products do not introduce new food compounds into the food supply and they have no unintended effects. Therefore, FDA states that they can be classified as GRAS because they are equivalent to traditional new varieties that historically have been given GRAS status. Only products that contain components that are significantly different in structure, function, and composition may be required to obtain a food additive regulation on a case-by-case basis. This option is a risk based option that requires extensive safety testing for products that are not normally found in the food supply, and less testing for products that contain substances already widely consumed. It places responsibility for the initial food safety assessment with industry. Lack of FDA oversight, especially for the first generation of biotechnology-derived food products, may raise public concerns. A number of public interest groups have indicated their opposition to this policy.

. *Option: Congress or FDA could establish a policy similar to the preliminary policy articulated by FDA, and include a formal notification procedure.*

Such a policy would require the establishment of a system for notifying FDA when a new transgenic crop is marketed. As currently outlined, FDA policy allows firms to determine if a new variety contains components that are already widely consumed. Thus, firms can make a determination about the GRAS status of new biotechnology products without consulting FDA. In the beginning, it is quite likely that most firms will consult FDA prior to marketing a new biotechnology-derived variety, but they are not required to do so. This situation is likely to create considerable apprehension among the public. Thus, a formal system of notification may be desirable.

The notification process could include safety data the company used to determine that the product was GRAS. Such data includes the identity of the host and donor organisms, information on the genetic construct, and information on the physiology of the gene product. Additional information required could include compositional data. A comparison of nutrient and toxic component levels in transgenic and counterpart traditional crops could be included, as well as data on allergens. This type of information will be available in the development of transgenic organisms and is required for a company to make its determination of the regulatory status of the product. Thus, requiring this information to be on record with FDA should not present undue burdens on industry. However, requiring FDA to review and act on this information for all transgenic crops will place a strain on the agency's re-

sources. Most likely FDA will need additional resources to implement this policy.

The notification process could be open to the public so that they can raise concerns and issues regarding transgenic organisms. It may also be useful for FDA to use an advisory committee to comment on the data presented. If an advisory committee is used, representatives from the public could be included along with technical representatives.

Such a policy might be effective for the safety assessment of the first biotechnology food products developed. It would allow FDA to provide at least minimal oversight over all biotechnology food products, assure the public that scientific information is available, and thus, might alleviate some public concern. In the short run, such a policy may appear to result in unnecessary regulation of these products. However, it may be the price industry must pay to have their products accepted by the public, at least in the initial stages of commercializing biotechnology food products.

. *Congress or FDA could require a food additive petition for all transgenic crops.*

This policy would force all transgenic food products to undergo a premarket safety approval process. It would only be based on a risk assumed to be inherent in the process of genetic engineering, an assumption not supported by scientific data. This policy would likely delay commercialization of transgenic crops already being developed and possibly could inhibit the development of additional transgenic crops. On the other hand, this policy would not be inconsistent with a broad interpretation of the food additive definition. And it probably would soothe some consumer fears and uncertainties about these products.

. *Congress or FDA could establish some categorical exclusions* ***of*** *transgenic food products from the requirement of a food additive petition, and could require all other biotechnology products to meet the requirements of a food additive petition.*

Once again categorical exclusions might include transgenic crops that do not contain components that are significantly different from those currently present in the food supply and for which unsafe, unintended components have not been introduced. This policy would be more risk based than requiring all transgenic organisms to meet the rigors of a food-additive petition, because transgenic organisms that are essentially the same as products that have historically been viewed as safe would not be required to undergo premarket approval. This policy would ease some of the burden on industry. There may still be public apprehension with respect to those products that have been excluded.

Ž Congress *or FDA could establish a policy in which the gene expression product is classified as a food additive if the same traditionally processed product would have been classified as such. It could exclude from the food additive definition gene products that would not have been classified as a food additive if produced by traditional means.*

Gene products that might be excluded as food additives are those that would code for agronomic functions such as drought resistance. This policy is based more on the intended use of the gene product rather than any safety risk that the gene product may pose, but would be consistent with how FDA has historically interpreted the food additive amendment. It would, however, be difficult to justify on scientific grounds.

. Congress *or FDA could establish a policy that the requirement for a food additive petition for transgenic organisms be determined on u case-by-case basis for each transgenic organism.*

Such a policy would allow FDA to provide oversight of all biotechnology products. This would provide the public with an assurance that all transgenic organisms would be reviewed by FDA. However, continuation of this type of policy indefinitely could overwhelm FDA, since the number of products that could be developed is large. At some point, FDA will likely need to categorize some products as GRAS, just as it does with chemical additives.

. ***Congress or*** *EPA could establish guidelines for the safety evaluation required to establish pesticide tolerances for whole plants.*

Currently, EPA does have guidelines for transgenic pesticidal microorganisms, but has yet to establish such guidelines for whole plants. Transgenic plants producing pesticidal compounds, such as Bt producing plants, are completing small-scale field trials. Guidance from EPA for dealing with such plants no longer can be delayed. Establishment of safety guidelines will require a new assessment paradigm (discussed later). Additionally. because States, FDA, and USDA enforce pesticide tolerances, EPA needs to work closely with appropriate agencies in establishing tolerances. EPA's work with States needs improvement in this area. Only recently has EPA even begun to compile a list of contact persons in State agencies. This ignoring of States could easily lead to State laws that are incompatible with Federal regulations, or

to gaps in State authority or expertise to carry out Federal regulations. Congressional hearings and oversight may be necessary if EPA does not improve this situation.

. *Congress or USDA -FSIS could establish guidelines concerning transgenic animals.*

USDA-FSIS plans to release guidelines in the near future concerning the slaughter of experimental animals in which gene transfer attempts failed. Guidelines concerning the slaughter of transgenic livestock are still in early draft form. Of particular interest will be guidelines concerning the slaughter and potential food use of transgenic animals that produce pharmaceuticals. FSIS and FDA have established a joint committee to deal with issues that jointly affect the two agencies. Careful monitoring of how successful this committee is may be required.

2. **Public confidence in the regulatory process needs to be enhanced. Making the regulatory process open and accessible to the public and above reproach is a key factor in providing trust and confidence in the decisionmaking process.**

. *Congress could direct agencies (FDA, USDA) to establish mechanisms to allow for increased public participation and to report their results to Congress within 1 year.*

This option sends a clear message to the agencies that Congress is concerned about the public's view of regulatory agencies and that the public should be more involved in the decisionmaking process. It gives maximum flexibility to the agencies to determine the method of incorporating the public's input.

A number of mechanisms are available. For example, Federal agencies could establish criteria by which local agencies can be notified any time significant risk or unique questions arise that are pertinent to them. Agencies may wish to adopt a procedure similar to that used by FIFRA, i.e., notification of petitions received, and if public interest warrants, an informal hearing. Increasing public participation will require increased resources and risk politicizing decisions, but could also enhance public confidence in the regulatory process. It might cost less in the long run.

. *Congress could direct the agencies to crease the use of advisory committees for decisions involving biotechnology and to change the composition of their membership to increase the number of nontechnical public representatives.*

For FDA, advisory committees could help establish GRAS and the minimum information needed for food additive applications of genetically engineered whole foods. These committees could be used as a first screening mechanism to see if a food additive petition is actually needed. Public meetings help assure the scientific validity of the process. EPA might also use advisory committees to establish tolerances for genetically engineered plants with pesticidal properties. This might be helpful since in-house expertise to handle this responsibility seems to be lacking. Advisory committees might also prove useful to USDA in establishing a policy on transgenic animals. The credibility of any advisory committee will be enhanced if it includes public representatives.

FDA may need to consider granting current nonvoting members of its advisory committees the right of full voting membership. And they may need to expand the list of technical fields beyond MDs from which experts are drawn.

Use of advisory committees presents some logistical problems and requires additional resources, but provides expertise that currently may be missing. Additionally, the possibility that non-technical representatives will pursue political agendas and unnecessarily delay committee decisions exists. However, used properly, such representatives can focus the attention of the committee on issues that might otherwise be overlooked and provide legitimacy to committee decisions.

● Congress *could direct the agencies (EPA, FDA, USDA) to change the notification procedures for advisory committee meetings.*

The standard method of notification for advisory committee meetings involves publication in the Federal Register. Few members of the public know what the Federal Register is, much less read it regularly. Also, notices published are written by and for those individuals knowledgeable in the field and, thus, the general public might not be clear as to what the issue is. Additionally, most meetings are held in Washington, DC. Agencies could have committees convene in different cities and publish announcements, other then the Federal Register, that are more likely to be noticed by a wider public. Such activities are likely to be more expensive than current ones, however, but make the decision-making process more accessible to the public.

. *Congress may wish to appoint a task force to study the role of independent safety testing of biotechnology products.*

Independent testing is unlikely to be popular with industry, however, a growing perception exists that companies are withholding negative data and that the safety

review **conducted by regulatory agencies is made without accurate and** complete data. Enhanced authority to subpoena data by regulatory agencies, most notably FDA, could be useful. Additionally, it may be worthwhile to consider establishing independent testing of products. FDA, for example, rather than companies could choose outside investigators to perform selected safety assessments, and these contractors could report results directly to FDA rather than the companies. A study to consider the broad range of implications of such a change would be warranted before implementation.

3. **Public interest groups argue that industry claims too much scientific data as confidential business information** (CBI), **and that this restricts the amount of health and safety data available to the public. Industry argues that there is too little protection of proprietary data and that this situation adversely affects their competitive position. Achieving the proper balance between protecting proprietary rights and disclosing health and safety data to the public is a delicate endeavor.**

● *congress could encourage FDA to publish more scientific review articles and hold public meetings in cases that generate public interest.*

Clearly it is possible for FDA to release considerable health and safety information to the public as it has done for bST. The public controversy surrounding this product apparently outweighed any competitive disadvantage presented to the firms producing bST. Such a policy might prove useful in responding to public concerns about other biotechnology products and potentially could enhance the accountability and credibility of FDA decisions.

. *Congress could conduct oversight to provide increased guidance to regulatory agencies attempting to encourage firms to reduce CM voluntarily.*

Congress could monitor whether health and safety data are being made available as products approach commercialization or if firms withdraw their voluntary cooperation and claim more data as CBI. If firms increase CBI claims, Congress could direct Federal agencies to require firms to justify CBI claims when a petition is submitted rather than waiting until a FOIA request is made. Currently, firms realize that it takes regulators longer to determine the validity of CBI claims than the time allotted to make regulatory decisions. This could encourage some firms to make CBI claims of data that in fact are not confidential.

Congress could also direct agencies to facilitate reconsideration of a decision if CBI data are released after a regulatory decision is made and causes public concern. Currently, firms can avoid public disclosure of data during the regulatory process simply by claiming confidentiality and know that the regulatory decision will not be reconsidered. If the decision is allowed to be reconsidered, firms may reduce their CBI claims.

Industry will oppose increased disclosure of safety data because it will erode their competitive position, On the other hand, with the current climate of public skepticism of new technologies and regulatory agencies, increased industry accountability and public disclosure of safety data may be required of business.

. *Congress could liberalize the CBI policy.*

Congress could direct FDA to release data it is currently authorized to release but generally does not. Congress could consider adopting a regulatory policy similar to that used in Canada which would weigh any harm to the company against the public's right to be informed about safety concerns. Current policy considers only the harm to firms. As a last resort, Congress could force the disclosure of health and safety data. Once again the potential harm to the competitive position of companies must be weighed against the public's right to be aware of potential safety risks and to regain public confidence in the regulatory process. Industry probably will object to an easing of CBI policy. Public support, on the other hand, may be equally strong for disclosure.

4. **Genetically modified foods will require a new paradigm for food safety evaluations. Changes in data needs, assay procedures, and sampling methodologies will be required.**

. *Congress could fund the development of new analytical methodologies and assay procedures through the National Institutes of Health (NIH).*

New analytical methods for whole food assessments must be developed if FDA is to determine the safety of genetically modified crops, and to monitor foods once they are marketed commercially. NIH, in coordination with FDA, could provide funding to develop food analytical technologies, These new technologies and assessment procedures would be useful in determining the safety of genetically engineered foods and could also enhance research programs such as the designer foods project (a component of cancer research) and nutritional programs.

. *Congress could provide funds to NIH for the development of databases detailing the normal range of nutritional and toxic components of food.*

Major nutrients and toxic substances in food have been identified, but additional information is needed to assess these food components, such as the quantities at which they normally are present in foods and their chronic impacts on humans. Assessment of such information will be needed to determine whether genetically modified foods present greater safety risks than do foods currently consumed.

. ***Congress*** *could direct FDA and EPA to request that assay procedures developed by firms to detect additives be readily adaptable for use under field conditions.*

Currently, when firms submit a food additive petition or a pesticide registration, they are required to provide an assay method to detect residues or additives in food. Generally, the method provided applies to a single residue and requires sophisticated instrumentation for identification and quantification. Agencies might require multiresidue assay methods that are more readily usable under field conditions than they are today. The residues would have to have some similar characteristics for a multiresidue technology to work. Development of such assay methods may create technical difficulties and are likely to create added costs for industry. However, they would improve monitoring and enforcement activities of regulatory agencies, an issue of particular importance to the public.

5. **Surveys clearly show that consumers desire additional information about the foods they consume. Labeling is a method to provide this information, especially for those concerned about foods produced from biotechnology.**

. *Congress could mandate that all food products containing constituents derived from biotechnology be so labeled.*

This would satisfy the desire of the public to be able to identify foods derived using biotechnology. But it probably would be expensive to provide labels and difficult to verify label information. No generic means exists today to identify whether a food constituent, such as a kernel of corn that will be ground into meal, has been genetically engineered or not, and it is unlikely that such a method can be developed. Consequently, genetically modified products would have to be kept segregated throughout the market to be able to assure the public as to whether their food contains such products or not. This is not now the case for many bulk commodities, such as grains, and entirely new marketing structures would need to be developed. Increased vertical integration of agricultural industries would likely occur. And, significant government resources would be needed to enforce mandatory labeling and the added expense would be passed along to consumers. Thus, guaranteeing that a product does not contain any products derived from biotechnology could become expensive. Based on current research, it is not clear that consumers would be willing to pay that added expense.

. Congress, *through research and extension agencies, could encourage niche markets to be established to satisfy the concerns of those willing to pay higher prices for labeled food signifying that it does not contain genetically engineered food.*

An alternative to passing the high cost of verification along to all consumers is to establish a higher priced niche market for biotechnology-free foods that would satisfy needs of some consumers. Such a market would be similar to the current organically produced food market. Organic produce is higher priced than traditionally grown produce but provides an alternative product to consumers who are willing and able to pay higher food prices. Recent legislation has been enacted to help resolve some problems involved with organic produce such as a lack of a standard definition, grower certification and oversight procedures. Such a policy might also work for biotechnology-free food products, and would have the advantage of passing the extra costs along only to consumers willing to bear them.

Public Sector Research

It is becoming increasingly difficult for the land-grant system to carry out its historic mission. In addition to the increasingly specialized nature of the research conducted, pressures from outside the system are building. Changing political support, resource base, and institutional frameworks combined with the development of revolutionary new technologies will put pressure on the land-grant system to change dramatically.

Historically, political support for the agricultural research system has come from the farm and rural population. For this reason, agricultural research has focused heavily on increasing the productivity of agriculture. However, this traditional base of support has been steadily eroding, and urban groups have put pressure on the system to shift research priorities to such areas as water quality, human nutrition, food safety, and sustainable agriculture.

The development of biotechnology and advanced computer technologies has the potential to revolutionize the way in which agricultural research is conducted, and to provide powerful tools to help address social problems. The scientists who conduct research using these technologies will need a thorough grounding in the basic disciplines that underlie them. Today only a small proportion of academic agricultural scientists have this background. Moreover, for advanced computer technology research to reach its potential, it will need to be identified as a research priority and universities must be encouraged to develop a promotion and tenure system that recognizes more than a publication record for research accomplishments. In addition, multidisciplinary teams involving basic computer sciences, systems design, and traditional agricultural sciences need to be encouraged. To this end, development of nationally recognized centers of excellence, similar to those developed for biotechnology, need to be considered.

In general, agricultural research is underfunded. Estimates of the social rate of return to public-sector agricultural research investments range from 35 to 145 percent, indicating a significant underinvestment in this type of activity by the public sector.

There has also been a slight, but potentially significant shift in the source of funding for agricultural research at land-grant universities (table 1-4). The States, which provide the majority of the funding for research at these universities, have been constrained in spending by the recession of the early 1990s. Few States have increased funds for research and many have cut funding in this area. USDA funding, the second largest single contributor to agricultural research, has remained basically stagnant, barely keeping up with inflation.

Funding from the private sector for university research, on the other hand, has been increasing in the form of industry-supported research, and from the sale of products by universities. Currently, these sources of income represent about 13 percent of the total funding for agricultural research, but have increased by 60 percent since 1982. The product sales category is a potentially lucrative source of funding for universities. Legal and institutional changes have made it easier for universities to capitalize on their research, since now they can retain title to any federally funded technology the university develops. Incentives to privatize the benefits of university innovation could shift the university further toward private funds, especially if public funds do not keep pace with increased needs.

Changing clientele, funding bases, technologies, and institutional structures will create new demands on the land-grant system. Decisions need to be made on how land-grant universities can best serve society in this new era.

Findings

The Uniqueness of Land-Grant Universities—Land-grant universities differ from other universities in their legislated mission to address research on the problems of society. Some argue that the land-grant system has, in part, already abandoned its mission, as agricultural researchers increasingly work for disciplinary laurels rather than society's benefit. Others argue that the system de-

Table 1-4—Total Research Funding for State Agricultural Experiment Stations, Selected Years[a]
(in millions of dollars)

Year	USDA[b]	USDA competitive	Other Federal[d]	State[e]	Industry	Product sales	Other[f]	Total
1982	161.3	5.5	77.8	522.2	57.0	58.5	70.0	952.3
1984	174.9	6.1	81.7	591.4	64.1	61.3	79.8	1,059.3
1986	174.4	11.9	110.8	704.3	78.1	62.9	89.8	1,232.1
1987	175.6	16.8	114.9	732.5	87.4	68.4	104.2	1,299.8
1988	187.0	19.3	115.0	770.0	91.2	77.8	114.1	1,374.2
1989	194.0	21.9	130.4	827.6	101.2	82.4	132.1	1,489.6
1990	203.6	20.0	143.9	877.9	113.8	91.6	145.7	1,596.5

[a]Funding is for the State Agricultural Experiment Stations only and does not include the 1890 universities, the Schools of Veterinary Medicine, or the Forestry Schools. Funding is in current dollars.
[b]USDA includes Hatch, McIntyre-Stennis, Special Grants, Evans-Allen, Animal Health, and miscellaneous other funds administered by the Cooperative State Research Service.
[c]USDA competitive is the USDA competitive grants program.
[d]other Federal includes funding from Federal agencies excluding USDA and includes funding from NIH, NSF, AID, DOD, DOE, NASA, TVA, HHS, PHS, etc.
[e]State is state appropriations.
[f]Other includes funding from nonprofit organizations, and contracts and cooperative agreements administered by USDA.

SOURCE: Inventory of Agricultural Research, Cooperative State Research Service, U.S. Department of Agriculture, Washington, DC, various years.

fines society's problems too narrowly, placing too much emphasis on increasing agricultural productivity and too little on nutrition, environmental, and rural problems among others. Some also argue that too much attention has been given to production agriculture and not enough to postharvest technologies, value-added products, consumer preferences, and agribusiness problems.

No easy answers exist as to what types of research should be conducted with public funds. What is clear, however, is that as the traditional clientele (i.e., farmers) continues to shrink. greater demands will be placed on the system to address the needs of other groups. To be able to do so may require some difficult choices concerning research mix, with some traditional research programs being eliminated and some new programs initiated.

Research Funding Based on Mission Functions—In recent years the land-grant system almost exclusively has embarked on a program to increase public funds through competitive grants. Relatively little attention has been given to securing other types of funding such as Hatch formula funds. This strategy is questionable for the land-grant system in the long run. Research conducted in conjunction with this study suggests that the most appropriate funding policy is a healthy mixture of formula funds and competitive grants. The results indicate that different funding mechanisms may be more appropriate for the different functions or goals of land-grant universities. For example, if the goal is to increase cutting-edge basic research, increased funding for competitive grants might be the best approach. If the primary goal is to enhance research applicable to problem solving or to train future researchers, the more stable and locally controlled Hatch formula funds may be the more appropriate mechanism. The appropriate allocation of these two types of grants depend on the relative priorities given to the three missions of land-grant universities.

Potential Privatization of Research at Land-Grant Universities—Two new sources of research funds are private sector investment and product sales. Constrained and basically stagnant research budgets provide many incentives for universities to increase funding via these mechanisms, but the development has raised many concerns. For example, incentives to privatize university innovations for the benefit of the university rather than society could conflict with the mandated mission of the university. Using public resources to reap private gains raises many ethical questions. Allowing individual researchers to share in the profits of their publicly funded work and encouraging universities to produce consumer products opens the door to potential abuses. Certainly, potential exists for conflicts of interest. There may be financial conflicts if individual researchers are allowed to capture the returns of their innovations. To some extent, this situation already exists in that researchers use public funds to generate new knowledge that can be sold to the private sector in the form of consulting fees. But there is a distinction between providing expertise to potentially multiple clients and having a vested interest in the development of one or several products by companies. Universities also may face conflicts of interest. The credibility of the university may suffer if it is viewed as being too cozy with industry. If public universities are viewed as being more concerned with their own private good than with the public welfare, then the public may not maintain its support for the university.

One underlying principal of scientific research is the free exchange of research results. Concern arises that with increased potential to earn income from research, the results of research will become more proprietary. Moreover, research results may not be freely or readily exchanged if a researcher, university, or industrial sponsor attempts to patent the results or seek additional private-sector funding.

Given the level of underinvestment in agricultural research and the stagnation of public-sector funding for this activity, the extra revenue earned from product sales could provide great benefits for the university and for society. Whether those benefits will be attained will depend on how the revenue generated from commercialized activities is used. The extra revenue could be used to fund socially underfunded research or to enhance the teaching capacity of the university. The new arrangements may enable universities to contribute to economic development in ways not previously possible. Whether or not the funds are used for such purposes will depend on how well university administrators are able to maintain a sense of priority for the overall research and teaching program, and whether they have the administrative skills to keep scarce resources allocated to the proper ends.

Policy Options

1. The new partnership between the public and private sectors potentially can revitalize agricultural research, but could also bias the overall research endeavor and damage the credibility of universities. Research and close monitoring will be needed to understand the changes occurring within the land-grant system and to ensure that they are not undermining the system as a whole.

. *Congress could require the U.S. Department of Agriculture to monitor the increased private-sector, funding of agricultural research and to prepare an annual report for Congress containing the data.*

Currently, little is known about the extent of private-sector funding at land-grant universities and the nature of the relationship between the universities and the private sector. Congress could conduct oversight hearings periodically on this issue. Furthermore, Congress could direct USDA to collect data from the land-grant universities on the extent of public-private collaboration, to prepare an annual report for Congress containing the data, and to provide guidelines on the appropriateness of various public-private sector research collaborations.

. *Congress could direct USDA to require land-grant universities to establish an explicit policy with regard to research sponsored by the private sector and report that policy to Congress.*

The USDA would require each university using private-sector research funds for agriculture to establish a specific policy as to how those funds are used based on a broad policy established by the land-grant system. Establishing an advisory board that includes members of the public in setting priorities for research funded from the private sector might be an effective mechanism. This would help to increase public confidence that the university is using funds to solve problems that confront society.

2. **High rates of return to public-sector investments have been reported by numerous studies, including past OTA reports. This indicates that public sector-research funding is below optimum rates.**

. Congress *could increase public-sector support of agricultural research.*

Increasing public-sector support of agricultural research might help to lessen the pressure on land-grant universities to obtain funds from the private sector. Given the high rate of return on public-sector funding of agricultural research, funding increases probably would prove beneficial.

. *Congress could maintain or decrease public-sector funding for agricultural research.*

Federal funding for agricultural research has been relatively flat for the last 30 years. As a consequence, States have picked up the increased costs of conducting agricultural research. It is difficult for States today to take on an ever increasing share of public supported research. If the Federal Government continues to reduce its contribution to research funding, land-grant universities must look for alternative sources of funding. Private-sector funding from specific industries or individual firms or product sales from technologies developed by the university are the most likely sources of additional research funds. The impact of this shift in support is not known but needs further analysis.

3. **Recent research indicates that public-sector funding mechanisms should be goal oriented.**

. *Congress could* ***appropriate funds for agricultural research through funding mechanisms*** *bused on well-defined agricultural research goals.*

The land-grant system provides teaching, extension, and research functions. Preliminary research suggests that Hatch formula funds are more suited to teaching and extension activities and competitive grants more suited to basic research. By appropriating funds according to goals to be achieved, Congress could improve the effective use of public funds.

. *Congress could maintain the current emphasis* of *increased funds for competitive grants and level or decreased funding of formula and intramural funds.*

Implicitly, this would indicate that Congress places greater emphasis on basic research than on adaptive research, extension, and teaching activities. Evidence does not exist that the lack of basic research is the primary constraint to the ability of land-grant universities to fulfill their historic mission of addressing research aimed at solving societal problems.

. Congress could extend ***competitive grants to extension and teaching curricula development.***

A strong case can be made for formula funding of agricultural research. However, if the only acceptable political form of increased funds is competitive grants, then expanding these grants to include adaptive research, extension and teaching could be considered. Balanced funding of basic research, adaptive research, teaching, and extension would significantly strengthen the land-grant universities and help them meet their multiple missions more effectively.

. *Congress could award* certain competitive grants to ***basic research that clearly shows ties to adaptive research.***

This would be a clear signal that Congress considers the original mission of land-grant universities to be appropriate today. Currently, most grants for basic research are not tied directly to adaptive research. Thus, it is

difficult to differentiate between funding provided by the National Science Foundation (the major funding agency for basic research) and the U.S. Department Agriculture.

4. **The public is increasingly losing confidence in land-grant universities' credibility, and credibility needs to be restored. Development of a more mission-oriented system with increased public input could help to restore confidence in the system.**

The OTA report *Agricultural Research and Technology Transfer Policies for the 1990s* addresses this issue in some detail and provides specific options that suggest changes in the system to make it more mission oriented. Those options are incorporated here by reference. Some of the options were incorporated into the 1990 Food, Agriculture, Conservation, and Trade Act of 1990(1990 Farm Bill).

SUMMARY

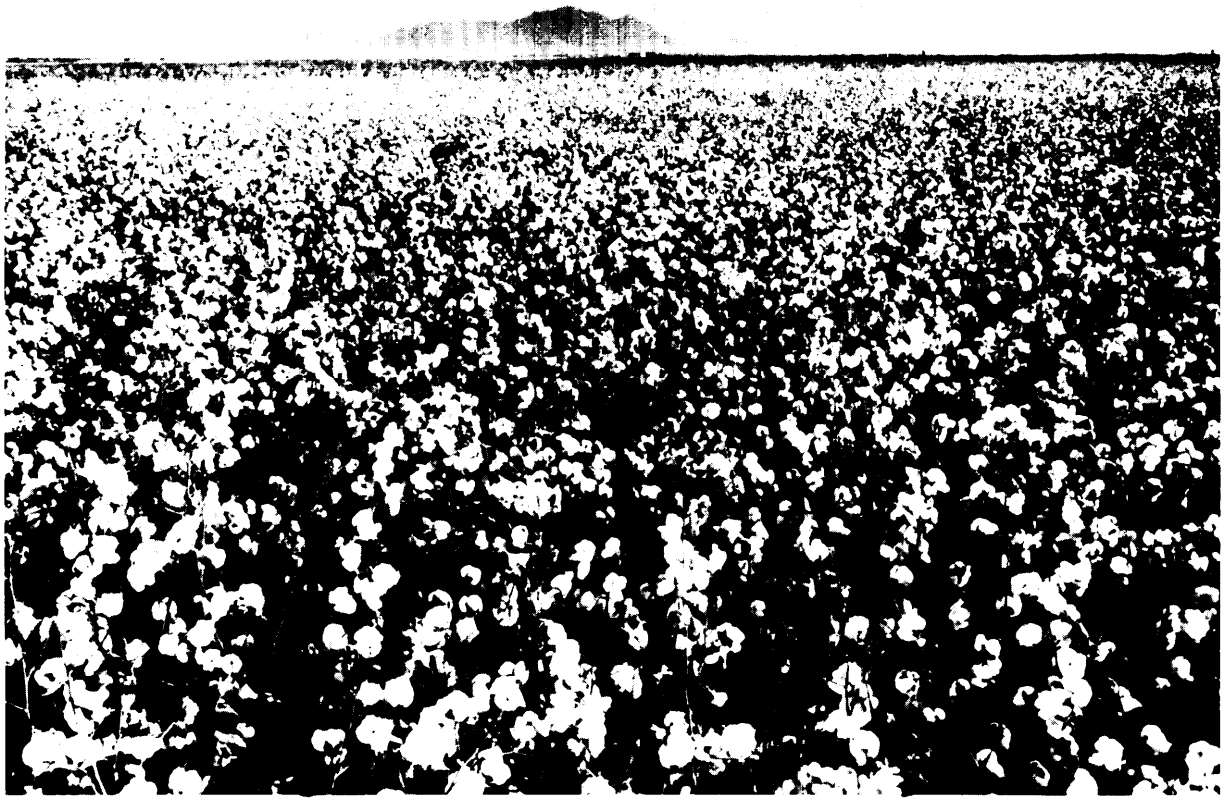
Newly emerging biotechnologies and information technologies hold great promise for American agriculture and can provide solutions to many problems. In the decade of the 90s, however, public concerns about the environment, food safety, industry structure, and institutions will focus on these emerging technologies. Whether these technologies will be accepted and flourish, or stagnate, will depend in large measure on how U.S. public institutions resolve the complex problems of regulatory oversight and on whether scientists and policy makers can allay public concerns about biotechnology in particular.

Part I

The Advancing Technologies

Chapter 2

Emerging Plant Technologies



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Emerging Plant Technologies

Each year in the United States weeds, insects, diseases, and poor weather conditions significantly lower crop yields. On average, major crop production in the United States achieves only about 22 percent of the yield theoretically possible under ideal conditions, based on genetic potential. Approximately 69 percent of this loss is due either to unfavorable climate and production using inappropriate farm management practices or poor soils. However, weeds, insects, and disease result in an annual average loss in total yield of 2.6, 2.6, and 4.1 percent respectively (6, 7, 8, 39). Seventy-one percent of crop insurance payments paid in the United States (from 1939 to 1978) were for crop losses caused by drought, excessive water, and cold (6, 8). The financial value of these losses is staggering.

Diseases in fruits, vegetables, grains, and oilseeds result in annual average losses in value of 17, 13, 11 and 13 percent respectively. For some highly perishable fruits, such as raspberries, blackberries, and cherries, losses from disease are estimated to be 38, 34, and 24 percent respectively of their total value. Annual losses in the United States due to viral diseases alone are estimated to be $1.5 to $2.0 billion dollars (5). A recent study estimated that crop diseases resulted in lost revenues equal to approximately 15 percent of the total crop in North Carolina. This value, if extrapolated to the United States as a whole, would result in losses of approximately $12.6 billion per year (8, 28). Loss in value due to weeds has been estimated at 10 to 20 percent of the total crop value; nearly $16 billion per year. Approximately $5 billion is spent annually to control weeds on farms and in rangelands, forests, and waterways (10, 26).

Traditional approaches to managing these problems have included the use of traditional breeding techniques to develop new crop varieties resistant to pests and better adapted to geoclimatic conditions. cultural practices, and the application of chemicals. Pest management is complicated by the fact that plant pests continuously adapt to new management techniques.

The need to develop new approaches to control plant pests is paramount. New pest management methods being developed focus on biological approaches, including the use of biotechnology to alter the plant genome and the use of biological control agents.

Approaches that focus on improving the plant's ability to withstand adversity in general involve genetically modifying the plant to have new characteristics. Scientists genetically modify organisms by altering or adding to an organism's genetic information with the intent to improve the physical characteristics of the organism. The genetic material of living organisms is composed of deoxyribonucleic acid (DNA).[1] The universal nature of genetic material enables scientists to transfer genetic material between species that are normally not sexually compatible, and can be used to modify microorganisms (e. g., bacteria, viruses, and fungi), animals, insects, and plants.

The genetic modification of plants can be accomplished using three different types of techniques: classical, cellular, and molecular (29). The classical methods of genetic modification include those associated with traditional plant breeding. Such methods include:

- fertilization of sexually compatible plants coupled with the preferential selection of those plants containing the desired characteristics,
- the use of chemicals or radiation to mutate the genetic material such that the mutated organism possesses preferred characteristics, and
- traditional cell culturing of plant sex cells such as anthers (the plant organelle that contains pollen) ovules, and embryos.

Cellular techniques involve regenerating a whole plant using culturing techniques, but unlike classical methods, the cellular techniques use tissue cells other than sex cells. Techniques include:

. cell fusion, in which two sexually incompatible plants are hybridized, and
. somaclonal variation,[2] which involves selecting plants that have been regenerated from undifferentiated plant cells—such plants often differ significantly from the parent plants.

[1] The exception to this statement are the viruses whose genetic material is composed of ribonucleic acid (RNA), rather than DNA.

[2] Plants arising from the culturing of undifferentiated cells often differ strikingly from each other and from the parent plant from which the culture was derived. In some unknown way, the process of culturing cells releases a pool of genetic diversity. **Possible explanations of this phenomena include chromosome breakage** and reunion, DNA rearrangement, and point mutations. The amount of variation that occurs is affected by some factors that can be controlled, such as the length of time the cells are cultured, the genotype of the tissue, the medium, and the culture conditions (15. 30).

The molecular techniques include those most commonly associated with biotechnology. Selected genes are isolated and transferred to a host organism using vectors (a piece of DNA that helps to incorporate a new gene into a host organism) or direct transfer techniques such as microinjection, electroporation, or particle guns. Molecular techniques allow for the transfer of selected genes between sexually incompatible species of the same type of organism, or between different types of organisms such as between plants and bacteria.

This chapter will focus on advances made in the use of biological methods to enhance crop production. Emphasis will be given to the use of molecular techniques and the use of biological control agents to enhance both pest resistance and the ability to improve crop production in less-than-ideal conditions.[3]

TOOLS AND TECHNIQUES OF BIOTECHNOLOGY

Biotechnology can be broadly defined as the use of living organisms to alter other organisms. In a practical sense, biotechnology is a set of tools that allow researchers to manipulate genetic material. These tools allow researchers to develop products that could not have been previously produced, and to explore new research questions that significantly expand our scientific knowledge. This section will describe some of the most important tools of biotechnology.

Biotechnology Techniques Used To Create Transgenic Plants

Transgenic crops are those crops whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm, using recombinant DNA techniques. The primary goals of transgenic crop research is to produce crops with improved ability to resist pests (i. e., disease, weeds, and insects); improved ability to grow under less-than-ideal soil and climate conditions; and to improve the quality characteristics of crops (e. g., by changing the oil composition of oilseed crops).

Many advances have been made that improve scientists' ability to create transgenic plants, and several major crops grown in the United States have been successfully transformed (table 2-1). Production of transgenic crops with improved characteristics, however, is constrained by insufficient knowledge of the appropriate genes for transfer; the knowledge base in plant biochemistry and physiology has not kept up with the development of molecular biology and transformation technologies.

To create a transgenic plant, scientists must:

1. isolate and purify the gene to be transferred,
2. find appropriate mechanisms (i.e., vectors or non-vector mechanisms) to transfer the gene into plant cells,
3. attach appropriate regulatory sequences to ensure proper expression of the new gene in the plant,
4. insert proper genetic markers to identify those cells that have been transformed, and
5. regenerate the transgenic cell or tissue into a complete plant.

Advances and methods used to accomplish each step will be described below.

Gene Identification, Isolation, and Purification

Isolating a single gene is complicated by the fact that a DNA sample obtained from a plant usually contains many genes. Researchers must be able to separate the one gene of interest from all of the other genes. Once isolated, the gene of interest is multiplied (cloned) to produce enough genetic material for subsequent uses. The process used to isolate and multiple the gene of interest is generally referred to as shotgun cloning because the process allows for the replication (cloning) of the entire genome (the sum of all genetic information contained in the chromosomes) of the organism.

A sample of DNA is first cut into small pieces, some of which may contain the desired gene. Special enzymes (restriction endonucleases) are used to cut the DNA at specific sites such that each piece has the same types of ends (figure 2-1). Pieces of DNA that have been cut with the same enzyme can be glued together regardless of the source of the DNA. This feature allows, for example, pieces of DNA from plants to be pasted together with DNA pieces from bacteria. It also allows scientists to paste DNA fragments into molecular vectors, pieces of DNA capable of inserting foreign genetic material into a cell. Scientists use vectors to help isolate and purify specific genes. Commonly used vectors include bacterial plasmids (circular pieces of DNA that can be easily in-

[3] Because of the large quantity of research on these technologies. this chapter will cite mainly OTA commissioned background papers and other review articles.

Table 2-1—Transgenic Crops Produced

Grains and oilseeds[a]	Fruits and vegetables	Other
Cotton	Tomato	Alfalfa
Rice	Sugar beet	White clover
Sunflower	Potato	Poplar
Soybean	Peas	Lotus
Rapeseed	Lettuce	Arabidopsis
Corn	Cucumber	Petunia
	Cabbage	Tobacco
	Asparagus	Walnut
	Carrot	
	Pear	
	Celery	

[a]Wheat and barley have not yet been successfully transformed, but it is anticipated that these crops will also be amenable to genetic engineering by the mid-1990s.

SOURCE: Office of Technology Assessment, 1992.

serted into bacterial cells where they can replicate) and bacteriophages (viruses that infect bacteria).[4]

To isolate a gene from an organism, the DNA sample of the organism is cut into many pieces, and all of these pieces are inserted into vectors (e.g., bacterial, plasmid, or bacteriophage). The vectors are then inserted into bacterial cells. As the bacteria reproduce, the vectors containing the pieces of the organism's DNA are also reproduced. This process results in the production of multiple copies of the organism's DNA, which is contained in the vectors. Now scientists have enough copies of genetic material to begin isolating the vectors that contain only the genes of interest. Isolation of the appropriate vectors is accomplished using a probe, a sequence of genetic material that recognizes the desired gene. The probe is used to identify the vectors containing the desired gene. These selected vectors can then be reintroduced into bacteria, where they are replicated many times to produce millions of copies of the desired genes. The desired gene can then be removed from the vector in quantities sufficient to perform subsequent genetic modifications (41).

The above procedure can be easily applied to organisms that possess small genomes, such as bacteria, but is more difficult to apply to more complex organisms such as plants, whose genome size is huge. Additionally, difficulties occur as a result of the lack of knowledge concerning the functions of many plant genes, which precludes the development of probes. Because of these difficulties, additional methods are being developed to improve the isolation of plant genes.

Restriction Fragment Length Polymorphism (RFLP) mapping is used to identify and clone plant genes and to further our understanding of the function of plant genes. RFLP maps take advantage of the fact that corresponding sites in the DNA of individual plants may differ as a result of mutations (referred to as polymorphisms). These polymorphisms can be identified and correlated with known markers (i. e., genes whose function have been identified), which helps to identify the general location of an unidentified gene (2 1). This procedure identifies the approximate location of a specific gene within the plant genome, which limits the amount of plant DNA that must be searched to isolate that specific gene. Once the general location of a specific gene is located, isolating the specific location of the gene depends on other methods still under developments RFLP maps are being made for corn, potato, tomato, rice, bean, pine, soybean, wheat, barley, sorghum, alfalfa, and Arabadopsis (27).

Mechanisms To Transfer Purified Genes Into Plant Cells

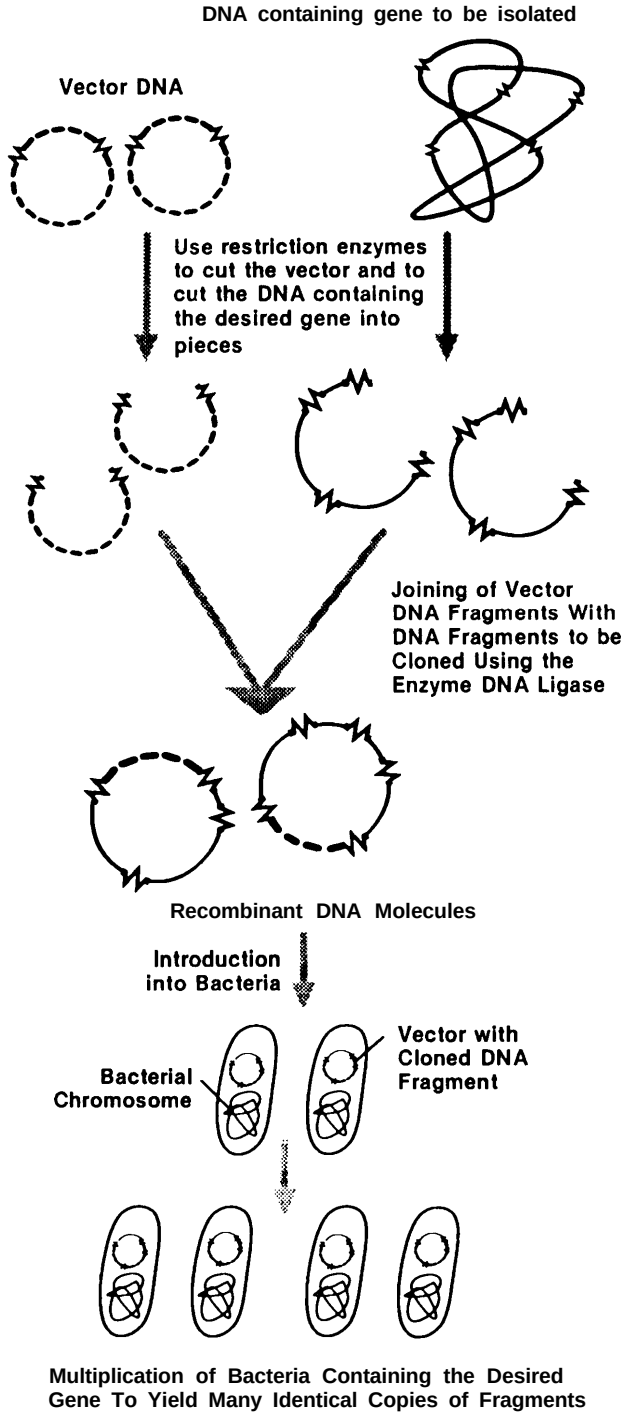
Once a gene has been isolated and purified, it can be transferred to create a transgenic plant. For many dicotyledonous plants (i. e., plants having two seed leaves (cotyledons) and net-veined leaves, such as soybeans), the Ti plasmid of certain strains of the soil bacterium *Agrobacterium tumefaciens is* commonly used as a vector to insert foreign genes into the plant. Unfortunately, Ti plasmids cannot be used to transform monocotyledonous plants (i.e., plants having a single cotyledon and parallel-veined leaves), which includes most of the major cereal crops (e. g., corn, rice, wheat) (27).

Vectorless methods have been developed to transform cereal crops. For example, chemicals (e. g., polyethylene glycol or calcium phosphate) and physical methods (e.g., electrical stimulation) are used to make plant cells leaky so that genetic material can flow in. These approaches have been used successfully to transfer foreign genes into rice and corn (27).

[4] Plasmids are commonly used to construct cDNA libraries (see ch. 3) and bacteriophages are used to construct genomic libraries.

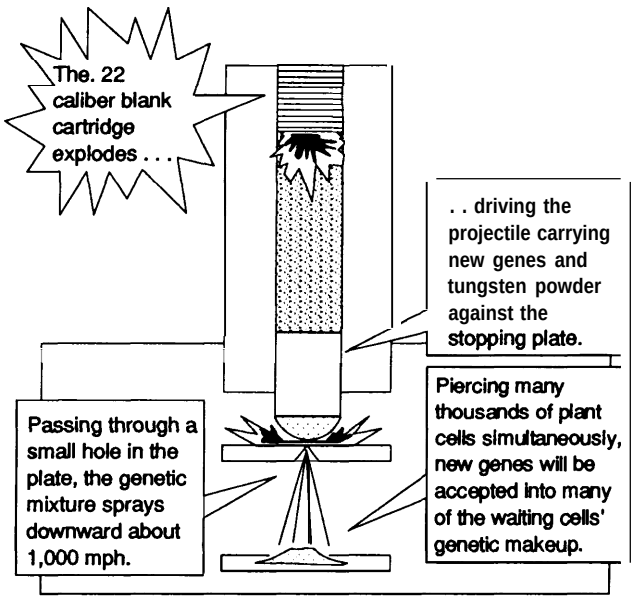
[5] Methods being developed include chromosome walking in which successively smaller overlapping portions of the RFLP fragment are isolated until one ''walks' to the desired gene. This method is constrained by the fact that RFLP fragments may still be too large to clone by the conventional methods described above (27). Another method is called gene tagging, which uses a transposon (a piece of DNA capable of moving around in the genome) to activate the gene of interest. The gene can be located by locating the transposon. Use of this method is inhibited by the size of the plant genome, the lack of transposons for many crops, and the fact that the transposon is often naturally present in multiple copies in crops (27).

Figure 2-1—Identification and Isolation of Desired Gene



SOURCE: Office of Technology Assessment, 1989

Figure 2-2—Gene Transfers With Bioblaster



SOURCE: Agricultural Research Service, U.S. Department of Agriculture

The bolistic method is an alternative vectorless method of gene transfer. This method uses a particle gun to shoot high-velocity microprojectiles coated with DNA into a plant (figure 2-2). It has been used to transfer genes to tobacco, soybean, and corn (27) and can be used to transfer genes to the plant cell nucleus (where the chromosomes are located) and potentially to other cell organelles that contain genetic material, such as the chloroplast (e. g., genes involved in photosynthesis) and the mitochondria (e. g., cytoplasmic male sterility genes used in the development of some hybrid crop varieties).

Currently, there is little control over where the foreign gene is inserted into the host plant. New methods are being developed to target the insertion site, but the frequency of success is low.

Use of Selectable Markers To Identify Transformed Plants

Cells that have foreign genes inserted need to be differentiated from those that have not been transformed. Scientists use markers to identify the transformed cells. The most commonly used marker is the kanamycin resistance gene. Cells containing this gene are resistant to the antibiotic kanamycin and will grow on a culture medium containing high levels of that antibiotic. Untransformed cells not containing the kanamycin resistance gene will not grow on this medium. Genes coding for herbicide tolerance can also be used as a selectable marker to differentiate transformed plants from those that have not been transformed.

Use of Promotors To Control the Expression of the Foreign Gene

Once a foreign gene has been incorporated into the genetic material of a plant, it must still function properly. Scientists use promotors (regulatory genes) to control when and where in the organism the gene is turned on. To date, most transgenic plants contain constitutive promotors, which means that the foreign gene is expressed equally in all tissues and at all development stages. Scientists are trying to isolate promotors that turn the inserted genes on only in specific tissues at certain development stages of the plant, and at a specific time. For example, it is desirable to direct the expression of insect tolerance genes only to the tissues eaten by the insect, such as leaves. The most commonly used plant promotor to date is derived from the cauliflower mosaic virus and is mostly constitutive. However, promotors that respond to light, heat, wounds, and oxygen deficiency, and that show tissue specificity for seeds, pollen, root nodules, and tubers are being identified (27). Understanding the molecular basis of promoter-mediated regulation of gene expression as well as isolation of promoters with varying specificities of expression is critical for the development of new generations of plant-based biotechnology products.

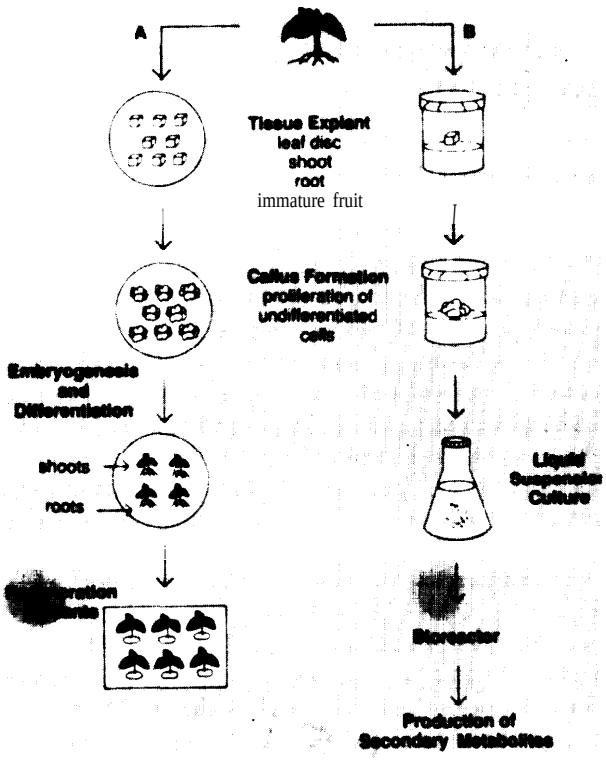
Use of Tissue Culture To Regenerate Transformed Plants

Once a plant cell or tissue has been genetically transformed, it must be regenerated into a complete plant. Advances in plant tissue culturing techniques have now made it possible to regenerate many of the most important crops (figure 2-3).

Early genetic modification research used protoplasm culturing to regenerate the transformed plant cells. Protoplasts are formed by enzymatically removing the outer wall of plant cells. These protoplasts are genetically transformed using the tools of biotechnology, then coaxed into forming a cell wall and eventually growing into a complete plant. However, such regeneration is difficult to achieve with many plant cells, which has lead to the development of callus culturing and cell-suspension methods.

Callus tissue cultures originate from tiny pieces of tissue snipped from seedling shoots or other appropriate plant parts. The tissue is placed in a petri dish containing plant hormones and other plant nutrients. The cells grow

Figure 2-3—Plant Tissue Culture Technology



SOURCE: S.K. Harlander, University of Minnesota

and divide, forming a mound of undifferentiated cells called a callus. When transferred to a regeneration medium, the cells in the callus differentiate into roots and shoots, which then grow into plants. Thousands of plants can be regenerated from one piece of tissue, but the process is labor intensive and expensive.

Methods for the growth of cell suspensions allow for the regeneration of plants from single cells rather than clumps of tissue. Tissues can be agitated in a flask containing a liquid medium, causing the cells to separate. In the appropriate medium, these cells will form somatic embryos that differentiate into entire plants. Embryo suspensions have been used to regenerate wheat, sorghum, and corn (27).

Callus culturing and cell-suspension methods allow for the use of a variety of plant tissues (e. g., leaves, stems, shoot tips, or cotyledons) from many plant species to be used to regenerate new plants. And, *Agrobacterium* particle gun technologies or other direct methods can be used to transform these tissues. Thus, most major crops can now be genetically engineered and regenerated to complete plants.

Other Biotechnology Techniques

Biotechnology is most closely identified with the use of recombinant DNA technologies to produce transgenic crops as described above. However, other technologies, some of which also involve the use of recombinant DNA, will also play a significant role in the development of new plant technologies. Some of these technologies are described below.

Antisense Technology

Antisense technology is a powerful research tool that enables scientists to study the physiology and development of organisms. It is also useful in the production of transgenic crops that have new characteristics (37). For example, this technology is being used to prevent softening in tomatoes (see *Biotechnology in Food Processing).* The power of the technique lies in its ability to eliminate or reduce the expression of a gene in an organism.

An analogy that might help to explain how this technology works is to view the expression of a gene as being similar to reading a sentence. For the sentence to make sense, it must be read in a certain direction; sentences that are read backwards, for instance, don't make sense. Gene expression is similar, A gene must be read in a certain direction to produce a gene product that makes sense to the organism (i. e., it is a functional compound).

The antisense technology consists of incorporating into an organism a synthetic gene that reads backwards (i. e., a product is made that doesn't make sense to the organism). The expression product of this backward-reading gene is a mirror image of the expression product of the same gene when it is read forward. When the expression products of the forward and backward genes meet,[6] they stick together, thus inactivating the product of the forward-reading gene (figure 2-4). Thus, the antisense technology can be used to inactivate selected genes in the plant. Use of the technique, however, is constrained by the need to know the precise nucleic acid sequence of at

[6]Technically, when a gene is expressed, it is first copied and modified to a second compound called messenger ribonucleic acid (mRNA). The mRNA then serves as the template for the subsequent production of proteins. It is the mRNA, rather than the protein, that meets and causes the inactivation.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

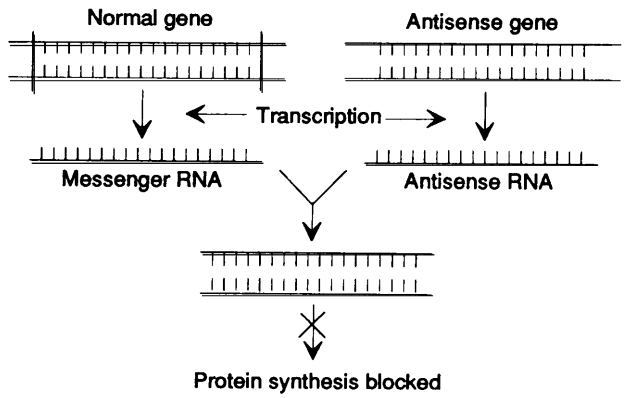
Molecular biologist at UC/USDA Plant Gene Expression Center successfully transferred new genes into cells of corn using a gene gun.

least a portion of the gene that codes for the expression product to be inhibited.

Polymerase Chain Reaction

The Polymerase Chain Reaction (PCR) technology enables scientists to rapidly generate large amounts of genetic material from a trace amount, which would otherwise be too small to analyze. PCR is an enzymatic process carried out in repeated cycles, each of which doubles the amount of DNA present. Small flanking sequences of DNA are identified on each end of the DNA sequence that is amplified. These flanking sequences are then used to create complementary strands of DNA that serve as primers. These primers are then annealed to the flanking sequences, and when appropriate enzymes and nucleic acids are added under the proper conditions, a new DNA strand is formed beginning at the primer and extending across the sequence of DNA to be replicated, such that a copy of this sequence is made. This methodology is rapid, sensitive, and relatively easy to carry out; about 25 cycles can be carried out in an hour. PCR reduces the difficulty of isolating and manipulating specific DNA

Figure 2-4—Antisense Technology



SOURCE: *Science* 253:510, 1991, p. 510.

sequences, and makes it possible to study biological problems related to very small amounts of genetic material (2).

Monoclonal Antibodies

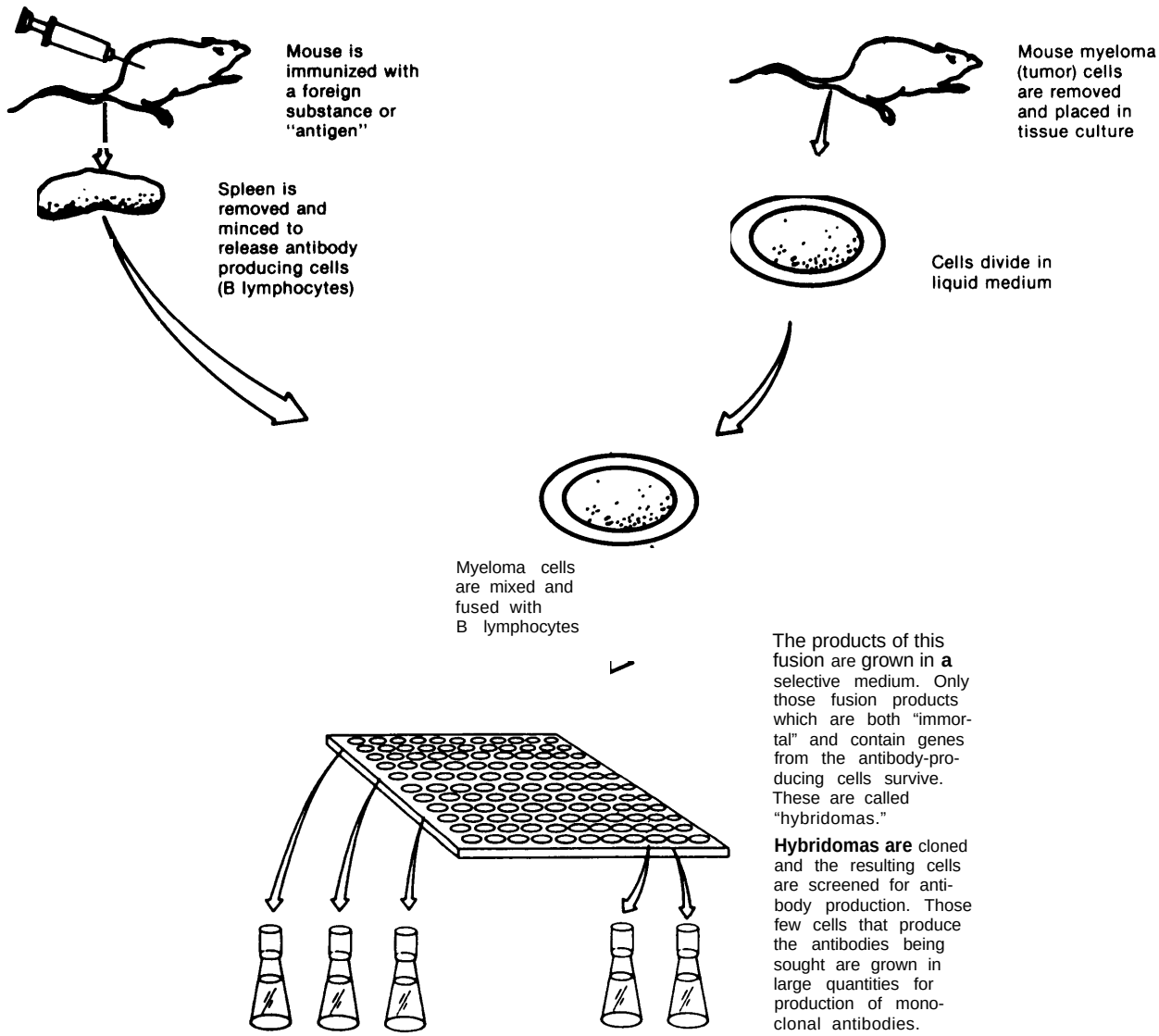
Monoclonal antibodies are identical antibodies that recognize a single, specific antigen (substance that elicits an immune response) and are produced by a clone of specialized cells. Their uses include the detection of residues and toxins in food, and as animal vaccines.

Monoclonal antibodies are produced by immunizing a donor animal (usually a mouse) with a target substance (figure 2-5). The animal's spleen is removed and dissociated into single-cell suspensions. These cells, some of which produce antibodies to the target substance, are removed to a nutrient medium. Spleen cells can survive only a few days in this medium, so to increase their life expectancy, the spleen cells are physically fused to a tumor cell, which can live indefinitely in tissue culture medium.[7] This fusion produces a hybrid cell containing the combined genetic information of both parental cells, which is capable of secreting the antibody produced by parental spleen cell and, like the parent tumor cell, can live indefinitely in culture medium.

This hybrid cell (called a hybridoma) can be isolated, cloned to ensure purity, and grown in mass culture where the secreted antibody accumulates in the culture medium.[8] The antibody (called a monoclonal antibody) that accumulates consists of a single antibody type rather than a mixture of antibody types (as occurs with traditional

[7] The spleen cells are fused in the presence of an agent, such a polyethylene glycol, to myeloma cells—tumors of B lymphocyte origin.
[8] Alternatively the hybrid cells can be grown as tumors in the peritoneal cavities of mice where very high levels of antibody accumulate in the ascites fluid surrounding the tumor.

Figure 2-5—Preparation of Monoclinal Antibodies



SOURCE: Office of Technology Assessment, 1988.

antibody production methods). It is this purity that makes monoclinal antibodies so useful.

Application of Biotechnology Techniques To Create Transgenic Plants

The tools of biotechnology are allowing researchers to explore new means to control plant diseases, insect pests, and weeds. Tissue culturing and genetic engineering, combined with traditional agricultural research methods, are allowing scientists to alter plants or biological control agents to achieve enhanced efficacy and host range in controlling plant pests. Biotechnology is also being used to improve a plant's ability to withstand environmental stresses, such as cold, drought, and frost, improve the shelf-life of fruits and vegetables and is being used to develop value-added products from agricultural commodities (e. g., increased carbohydrates. modified oils, and proteins that contain essential amino acids). In addition to developing new products, the tools of biotech-

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Plant molecular biologist examines successful results of the cloning of a gene necessary for plants to synthesize ethylene, the ripening hormone. More recently, scientists have blocked this gene, producing genetically engineered tomatoes that ripen on demand.

Photo credit: Monsanto Co.

Tomato plants that show one stripped by caterpillars and one not. The plant not stripped contains the *Bacillus thuringiensis* toxin gene.

nology are expanding the knowledge base of plant resistance and the interactions of plants, pests, and biological control agents with the rest of the ecosystem.

Genetic Engineering of Plants for Insect Control

Traditional breeding programs have successfully produced varieties of alfalfa, cotton, corn, rice, sorghum, soybean, and wheat that have been resistant to, or tolerant of, key pests and will continue to play an important role in developing insect resistant plants for some time in the future. However, the tools of biotechnology have created the possibility of selectively engineering plants for insect resistance. Biotechnology will permit the transfer of resistance genes into plant species for which the resistance gene is not inherent. Biotechnology is also being used to improve the understanding of mechanisms by which plants are resistant to insects.

Few genes known to produce insecticidal proteins have been identified. Candidate genes must code for proteins that are stable in the plant cell, are not rapidly digested when consumed by insects, have high activity against feeding target insects, and are safe for nontarget invertebrates and animals. Insecticidal proteins produced by the spore-forming bacteria *Bacillus thuringiensis* (Bt) are among the few known to meet these criteria,

The Bt bacteria produces crystals that contain compounds toxic to insects. Insects feeding on plants contaminated with Bt bacteria ingest the crystals, which are dissolved in the insect midgut, releasing the protein toxins. Different strains of the Bt bacteria produce insecticidal toxins specific to Lepidoptera (butterflies and moths) only, to Diptera (flies and mosquitoes) only, to Coleoptera (beetles) only, and to both Lepidoptera and Diptera.

Genetic engineering is being used to improve the delivery of the Bt toxin to insect pests by incorporating the insecticidal gene into other vectors (see Biological Control of Anthropoids: Pathogens) or by transferring the insecticidal gene directly to plants. Genes coding for the Bt insecticidal protein have been cloned and inserted into tobacco, tomato, and cotton plants among others (1). Transgenic plants producing Bt insecticide are expected to be commercially available by the mid to late 1990s.

Genes for some insect trypsin inhibitors have also been cloned. Trypsin inhibitors are compounds that, when present in large amounts, may reduce the ability of an insect to digest plant material. Some plants, such as the seeds of cowpeas and beans, contain large quantities of trypsin inhibitors (i.e., 1 to 2 percent of the total protein), and the levels in plant leaves may be increased in response to mechanical damage or insect feeding. Trypsin inhibitor genes derived from tomatoes have successfully controlled the growth of insect larvae when transferred to tobacco plants. Transgenic plants genetically engineered to produce trypsin inhibitors may be available by the end of the decade (1).

Genes that code for lectins and for arcelin are also potential candidates to confer insect resistance to transgenic crops. Lectins are sugar-binding proteins found in the seeds of peas and common beans. They are effective against bean weevils and cabbage weevils. Arcelin is

produced in the seeds of wild beans and is toxic to bean bruchid pests (1).

Genes coding for insecticidal proteins other than Bt toxins and trypsin inhibitors must be identified. RFLP maps are being used in tomatoes, for example, to discover the location of insect resistance genes in plants. The development of tissue-specific promotor sequences and promotors that respond to selected environmental stimuli are needed to improve the efficacy of insect control.

Genetic Engineering of Plants for Weed Control

The presence of weeds in crops decreases productivity and crop quality. To control weeds, farmers commonly apply herbicides. Most herbicides act by inhibiting key enzymes in photosynthesis or other essential plant biosynthetic pathways. Plant species respond differently to herbicides depending on the sensitivity of plant enzymes to the herbicide or the ability of the plant to metabolically inactivate the herbicide. These abilities explain why herbicides are often effective against either grassy or broadleaf plants, but not both (26).

Herbicide manufacturers would like to develop broad-spectrum herbicides active against all economically important weeds, but their efforts have be constrained because broad-spectrum herbicides not only kill weeds, but they injure crops as well. Two approaches have been taken to minimize crop damage when using broad-spectrum herbicides. One approach is to use herbicide antidotes, compounds that enhance the metabolic inactivation of herbicides in plants (19, 20). Few such antidotes have been discovered, however, and it is unlikely that this approach will yield significant success in the near future. The alternative approach is to develop crop varieties that are resistant to the herbicide used.

Traditional methods have been used successfully to develop herbicide-tolerant crops. Tissue culture and plant regeneration techniques have produced tobacco and soybean varieties tolerant to sulfonylurea herbicides and corn varieties tolerant of imidazolinone. Attempts to develop herbicide-tolerant crops using tissue-culture techniques are most successful when the herbicide affects only one compound in a plant biosynthetic pathway (i. e., it has a single target site) and a mutation in that compound confers herbicide tolerance without affecting the growth of the plant, or when the mutation of a single plant gene increases the ability of the plant to inactive the herbicide or to absorb less of the herbicide. Use of these methods is constrained by the lack of naturally occurring herbicide tolerance genes in crops (26).

Genetic engineering techniques overcome the lack of naturally occurring herbicide resistance genes in plants by allowing for the transfer of these genes between crop species. Thus, crops tolerant to a specific herbicide (but not all herbicides) can be developed. Three different approaches have been taken to engineer crops successfully for herbicide tolerance, the first of which are expected to be commercially available by the mid 1990s (table 2-2). One approach relies on making the crop produce excess quantities of the enzyme normally affected by the herbicide. By producing an excess quantity of the enzyme, a sufficient quantity is still available to catalyze important plant biosynthetic pathways even though some of the enzyme has been inactivated by the herbicide. Excess production can be achieved by inserting several copies of the gene coding for the enzyme into the plant, or by using promotor sequences that cause excessive expression of the genes coding for the enzyme, This method has been used successfully to produce crops tolerant to glyphosate and phosphinothricin (26).

The most commonly used approach to produce crops tolerant to herbicides is to alter the gene coding for the enzyme affected by the herbicide in such a way that the resulting altered enzyme is still effective in the plant, but is not inactivated by the herbicide. This altered gene is then inserted into the plant where it produces an altered enzyme that confers herbicide tolerance. This approach has been used to produce crops tolerant to glyphosate, sulfonylureas, phosphinorthricin, atrazine, and imidazolinone.

The third approach is to transfer to plants those genes that code for enzymes that inactivate herbicides. This approach has been taken to confer plant tolerance to bromoxynil, 2,4-D, and phophinothricin.

An alternative approach to weed control is to develop crops that produce their own herbicides. These plant-produced herbicides, called allelochemicals, can be either volatile organic compounds released into the air or soil where they can be absorbed by the weed or nonvolatile organic compounds released as root exudates or leachates of other organs, such as seeds. Most volatile allelochemicals are terpenoids whose secretion increases with rising temperatures, while most nonvolatile allelochemicals are aromatic chemicals (26). Significant research is still needed before crops can be engineered to produce allelochemicals. Alternatively, it may be possible to identify and use plants known to naturally produce allelochemicals as cover crops or in low tillage

Table 2-2—Current Targets for Crop Modification for Herbicide Tolerance

Herbicide	Research institution	Commercial introduction	Weed/crop targets
Atrazine	Ciba Geigy, Inc	Not expected to be commercialized	NA
Bromoxynil	Calgene, Rhone-Poulenc	Mid 1990s	Broadleaf/dicots
Betanal	Schering	Late 1990s	Broadleaf/sugar beet
2,4-D	Max Planck	Not a commercial target	NA
Dicamba	Sandoz	Late 1990s	Broadleaf/NA
Glyphosate	Monanto, Calgene	Mid 1990s	Broad spectrum soybean, rape, cotton, corn
Imazapyr	American Cyanamid Molecular Genetics	Early to mid 1990s	Broad spectrum/corn
Metribuzin	Mobay	Late 1990s	Broad spectrum/ soybean
Basta	Hoechst	Mid 1990s	Broad spectrum/ rape, beet, potato, soybean, corn
Sulfonyl ureas	DuPont	Mid 1990s	Broad spectrum/ soybean, rape

NA = Not applicable.

SOURCE: Off Ice of Technology Assessment, 1992

situations to control weeds. For example, it has been shown that certain cucumber strains produce compounds toxic to the weeds proso millet and barnyard grass under field conditions. The possibility of using alleochemical-producing plants is also being explored in fruit production (33).

Understanding the nature of allelochemicals in addition to the advances that have been made in elucidating the mechanisms of herbicide action is expected to enhance the design of future herbicides.

Genetic Engineering of Plants for Disease Control

Bacteria, fungi, parasitic seed plants, nematodes, insects, and viruses, among other organisms, can destructively alter the structure or physiological processes of plants, resulting in disease. However, plants possess the ability to resist the invasion of pathogenic organisms. All of the plants of a species can be resistant to a pathogen, or certain varieties of a plant species can be resistant to a subspecies of the pathogen (i. e., cultivar specificity). The interaction of bacterial and fungal pathogens with plants is helping to elucidate the mechanisms by which plants resist pathogenic organisms **(27).**

The ability of plants to resist pathogenic organisms involves the complex interaction of genes in both the plant and the pathogen. The interaction of compounds produced by plant resistance genes and genes in the pathogen (i. e., avirulence genes) triggers a hypersensitive response. Plant cells initially infected by the pathogen die, preventing the spread of the pathogen to the rest of the plant. Thus, the pathogenic effects remain localized at the site of initial infection, and disease is prevented from spreading throughout the plant.

The mechanisms by which pathogens infect plants are also being elucidated. Pathogenic microorganisms contain pathogenicity genes that produce compounds toxic to the plant and/or allow the pathogen to attach to the plant, penetrate the cuticle and degrade the walls of plant cells, and degrade chemicals produced by the plant in its own defense. These pathogenicity genes can be activated by signals from the plant itself. For example, the presence of cell wall degradation products in plants can trigger the production of enzymes in some pathogenic fungi that degrade the cell wall. In a similar manner, compounds produced by pathogens trigger a response by the plant to the pathogen. Plant defense genes are stimulated to produce compounds that may be toxic to pathogens, reinforce the cell wall, and/or inhibit enzymes produced by the pathogen (27).

Efforts are underway to clone and characterize pathogen and plant genes involved with resistance. To date, no plant resistance genes have been cloned, however, avirulence genes from bacteria and viruses but not fungi, have been. Additionally, few plant defense genes have been identified and cloned. Only the gene coding for chitinase, a compound that is toxic to fungi, has been shown to confer disease resistance when transferred to tobacco. Also a compound derived from moths, when

Photo credit: Richard Nelson, Samual Roberts Noble Foundation.

Transgenic tomato plant expressing the coat protein gene of tobacco mosaic virus (left) and control plant (right).

transferred to tobacco, decreased the severity of an infection by the bacteria *Pseudomonas solanacearum.* Given the **state** of the art, it is highly unlikely that plants resistant to bacteria and fungi will be developed before the year 2000 (27).

Greater success has been achieved in developing plants resistant to viruses. Plants have long been known to display cross protection, a phenomena that occurs when plants infected with a mild strain of a virus do not develop severe symptoms when challenged with a stronger strain of the same virus. Cross protection is comparable to immunity in animals, although plants do not have immune systems and the mechanism of protection differs. Although cross protection has been achieved in plants by inoculating individual plants with a mild virus strain, this process is very labor intensive and carries a small risk that the virus strain used will become more virulent and act in a synergistic fashion with other viruses (27).

Genetic engineering has been used to avoid these problems. Genes coding for virus coat proteins (i.e., the proteins that make up the shell that surrounds viruses), other

Table 2-3—Virus Coat Proteins Engineered Into Plants

Alfalfa mosaic virus
Cucumber mosaic virus
Potato viruses S, Y, and X
Potato leaf roll virus
Tobacco mosaic virus
Tomato mosaic virus
Tobacco rattle virus
Tobacco streak virus
Soybean mosaic virus
Papaya ringspot virus
Tomato spotted wilt virus

SOURCE: Office of Technology Assessment, 1992.

virus proteins, and virus RNA sequences can be introduced into plants to elicit a resistance response (3, 4). Plants engineered with coat protein genes from a specific virus have resisted subsequent infection by the same virus, and in some cases to related viruses having similar coat proteins. Currently, many viral coat protein genes from different plant viruses have been transferred to plants to confer resistance (table 2-3) (4). The mechanism by which protection occurs is not fully understood. Most evidence suggests that the accumulation of viral coat proteins in plant cells interferes with the release of viral RNA needed to initiate infection (4).

In addition to viral coat proteins, other viral genes have been transferred to plants. Those having potential for virus control include: genes for virus replication, antisense RNA, satellite RNA, and ribozymes. The antisense technology has also been used to inhibit viruses in plants. Other approaches include transferring satellite RNA sequences (small RNA sequences that depend on helper viruses to replicate and package new virus particles) to plants where they have protected the plant from developing symptoms in response to an infection by the helper virus. Genes coding for RNA sequences that act like enzymes (i.e., ribozymes) have also been transferred to plants where they have cleaved invading viruses (27).

Genetically engineered dicotyledonous plants resistant to certain viruses are expected to be commercially available by the mid 1990s. Monocotyledonous plants resistant to viruses will probably not be available until the late 1990s or early the next century. Currently, only a few genes with potential for controlling fungi and bacteria have been identified, cloned, and introduced into plants (see table 2-4).

Genetic Engineering of Plants for Thermal and Water Stress Tolerance

Progress in improving the tolerance of plants to water and thermal stress will depend, in part, on better ways

Table 2-4—Disease Resistance Genes Introduced Into Plants

Disease pathogen	Gene/plant
Fungal	Chitinase/tobacco
Bacteria	Antibacterial protein from moth/ tobacco, potato
	Enzyme to detoxify bacterial toxin
Viral	Viral coat protein
	Other virus genes
	Satellite RNA
	RNA enzyme (ribozyme)
	Antisense RNA

SOURCE: Office of Technology Assessment, 1992

of defining and quantifying these stresses as well as nonstress states. Defining these stresses is further complicated by the fact that water stress and temperature stress are not easily separated, particularly at high temperatures. New tools, such as remote and contact sensing,[9] are being developed to detect plant stress (9).

The lack of detailed knowledge of the physiology of water and temperature stress tolerance also constrains progress in this field. The root system of the plant exerts major control over water uptake. Little research has been conducted to measure root response to water and thermal stress. Most measurement techniques used to date are disruptive if not destructive to root systems. New techniques are needed to determine factors that affect the distribution of roots in the soil and the ability of the roots to absorb water and transport that water through the vascular tissues of the plant (9).

Plant-cell culturing, combined with selection for enhanced ability to adjust the salt and water concentration of plant cells (osmotic pressure), has been shown to be effective in improving drought tolerance. However, while improved sensitivity to osmotic pressure has increased the survival of the plant, it does so at the expense of plant growth and yields (34).

Some plants contain genes that code for proteins conferring tolerance to extremes of temperature or drought; these genes are possible candidates for isolation and transfer to other plants through genetic engineering techniques. For example, tobacco cells that are exposed to gradually higher levels of salt synthesize several novel proteins. One such protein is osmotin, whose synthesis is regulated by several mechanisms, including exposure to low water environments or changes in endogenous levels of the hormone abscisic acid (ABA). ABA is known to lower the rate of transpiration from leaves and prevent water loss. The role of osmotin in cellular osmoregulation is now under investigation (9).

Some plants, when challenged by elevated temperatures, produce heat shock proteins. Genes coding for several of these proteins have been sequenced and their promoter regions identified. However, the metabolic functions of most of these proteins are not understood, and this constrains their use in biotechnology to improve plant tolerance to elevated temperatures (9).

In general, the fundamental research needed to understand the mechanisms of tolerance to thermal and water stress simply has not kept pace with the development of biotechnology tools, and thus, scientists do not currently know what genes to transfer into plants to improve tolerance for these stresses. Thus, genetically engineered plants tolerant to elevated thermal or water stress are unlikely to be developed within this decade. However, antifreeze proteins have been transferred to plants and production of plants with improved cold tolerance may become available within 10 to 15 years. Plants transgenic for antifreeze proteins have the potential to improve cold hardiness by lowering the temperature at which leaves freeze (12, 17). Antifreeze proteins from fish are also being used to improve the post-harvest freezing and thawing qualities of fruits and vegetables by inhibiting ice recrystallization in tissues (22).

Biotechnology in the Food Processing Industry

Historically, the food processing industry has had to accept and adapt to heterogeneous raw materials. Biotechnology can be used to better tailor food crops to meet food processing and consumer needs. Tissue-culture techniques are being used to select or construct crop varieties with improved functional, processing, or nutritional characteristics (table 2-5).

Plant tissue-culture techniques can be used to produce food flavor and coloring ingredients. These methods could potentially replace production and extraction of these ingredients from plants (15, 18). For example, a private company recently has succeeded in using tissue culture techniques to produce vanilla (14).

[9]Contact sensing requires contact with plant tissues and may require destruction of at least part of the plant. It involves the direct determination of the state of a physical, biological, or chemical quantity. Remote sensing quantitates parameters measured by using a sensor to detect electromagnetic waves emitted or reflected by plants.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Framed by drought-dried cornstalks, drought-resistant lima beans stand tall and lush in test plot. Scientists hope that genetic engineering researchers can isolate the genes that give the lima bean such a high degree of drought tolerance.

Table 2-5—Use of Tissue Culture To Improve Food Characteristics

Crop	Characteristic
Tomato	Increased solids
	Increased shelf life
Carrots	Increased sweetness, crunchiness
Celery	Decreased stringiness
Corn	Improved amino acid composition
Rapeseed	Decreased saturated fatty acids

SOURCE: Office of Technology Assessment, 1992.

Genetic engineering is also a means of altering food characteristics. Genes coding for enzymes involved in starch and lipid biosynthesis are being isolated and cloned, enhancing the prospects of engineering plants with specific composition of starch and oil. Genes coding for floral pigment pathways are also being isolated. Plants potentially can be engineered to produce pharmaceuticals such as blood clotting factors and growth hormones. For example, oilseed rapeseed has been genetically engineered to produce enkephalins (40). In addition, antisense technology is being used to eliminate toxins allergenic compounds, or off-flavor components in plants, and to delay ripening of tomatoes (15).

Photo credit: DNA Plant Technologies, Inc.

Vegi Snax is an example of successful application of plant tissue culture for selection of crop varieties with improved functional, processing, and nutritional characteristics.

Biotechnology is also being used to improve microorganisms used as vegetable starter cultures and in brewing and baking (i.e., organisms used in making sauerkraut, pickles, olives, soysauce, wine, beer, and bread) such that these organisms tolerate different temperature and pH ranges. Similar work is being conducted with microorganisms used to produce food ingredients such as acetic acid, citric acid, niasin, vitamin B 12, xantham gum, and monosodium glutamate. In addition, genetically engineered enzymes are being developed to treat food processing wastes (18).

Finally, biotechnology is being used to develop methods to assay levels of pathogens, toxins, and chemical contaminants in raw ingredients and final products. DNA probes and poly and monoclinal antibody kits are beginning to replace traditional bioassay methods. For example, many of the assay procedures used to detect pesticide residues in food are monoclinal antibody kits (18).

THE TOOLS AND TECHNIQUES OF BIOLOGICAL CONTROL

Approaches Used in Biological Control

Biological control of pests relies on using living natural enemies (e. g., parasites, predators, and pathogens) to reduce pest populations to levels lower than would otherwise

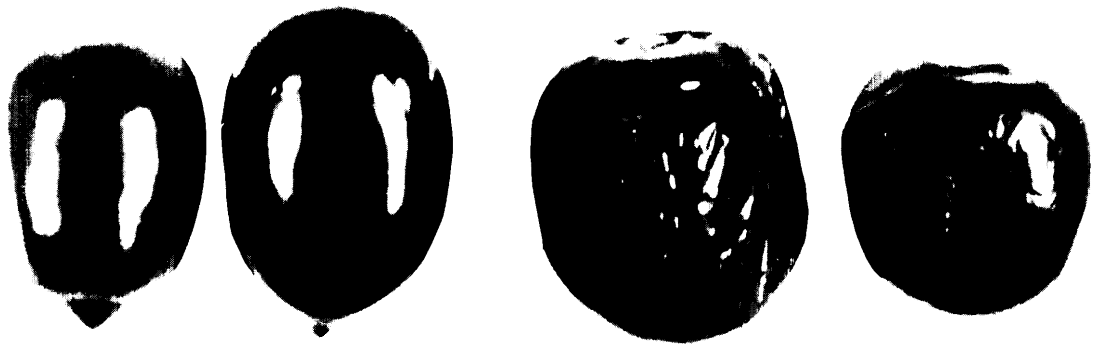


Photo credit: Calgene, Inc.

Antisense tomatoes (left) and control (right) 3 weeks after harvest.

occur (13). Parasitic organisms are those whose development takes place in or on a single host organism; predator organisms are those that consume other organisms as a food source; and pathogenic organisms are those that cause disease in other organisms. Many organisms, including insects and other arthropods (e. g., spiders and mites), bacteria (and related organisms such as rickettsiae and mycopiasmas), viruses, fungi, protozoa, and nematodes are being used as biological control agents to manage weeds, insects, and other arthropod pests, as well as disease organisms in economically important plant species. Biological control methods have been used in the United States on a limited basis for at least 100 years. Approaches used can be classified into three common types-the classical approach, augmentation, and conservation (25).

Biological control agents used to control nonindigenous pests, particularly those introduced from other countries, is called the classical approach. When a non-native pest is introduced into a new environment, often there are no natural enemies to control that pest. The classical approach searches the area of origin of the pest and identifies natural enemies. These natural enemies are then introduced into the new environment to control the pest (25). Attempts are made to establish the introduced natural enemies as part of the ecosystem so that pest suppression will be permanent.

The augmentation approach focuses on increasing the existing population of indigenous pest enemies. Small numbers of natural enemies can be released periodically, as needed, to increase the indigenous population to levels sufficient to control pest numbers at levels below those that cause serious economic problems. The newly released natural enemies are expected to become part of the ecosystem, and to help suppress more than one generation of pests (25). This approach is similar to administering a booster shot to augment indigenous-pest enemy populations.

Alternatively, large numbers of natural enemies can be released at one time with the intent of quickly suppressing the pest population by creating an epidemic-like situation. The control agent (i. e., natural enemy) is not expected to become a permanent part of the ecosystem and the natural enemy is not expected to control more than one generation of the pest. The natural organisms used with this approach are **usually microorganisms,** such as bacteria and fungi. They are manufactured, formulated, standardized, packaged, registered as pesticides, and applied to pests using methods and tools similar to those used for chemical pesticides. **Because** of these similarities to chemical pesticides, this strategy is often referred to as the microbial pesticide or inundative approach to augmentation. This approach generally requires regular application because the control agents do not survive between crop seasons. or survive in insufficient number to be effective the next season, or are prevented by other factors from causing significant disease in the pest population (10, 16).

Conservation practices can be used to protect and maintain natural enemy populations by manipulating the environment. such as altering cropping patterns and farm management practices to enhance the indigenous population, maintaining refuges and providing feeding and nesting sites for natural enemies, and by applying pes-

ticides only when pest populations exceed specified levels (16, 25, 35).

In general, the classical method of biological control has been the approach most frequently and successfully used to control weeds, insects, and other arthropods in the United States. This is perhaps not surprising given the large number of pests that are of foreign origin. For example, an estimated 39 percent of the 600 most important arthropod pests in the United States are of foreign origin and more than 630 additional foreign arthropods are on the list of lesser pests (36). Based on past history, it is predicted that exotic arthropod species will continue to be added at a rate of about 11 species per year and that approximately 7 of those species will become significant pests. Clearly the classical approach will continue to be a major biological control methodology.

Biological control approaches have had limited success against pests in grain and row crops.[10] Biological control has been most successful against naturalized permanent pests in areas of low disturbance (such as rangeland, pastures, forests, and some aquatic habitats) where the targeted pest is the dominant species, and where the end goal is a stable plant community. The poor record of success in grain and row crops is often attributed to the fact that grain crops only persist for short periods of time, during which the natural enemy must discover the crop and become established, must find and attack its host pest, and must increase its population to numbers sufficient to reduce the pest population significantly. The abrupt end of the crop season precludes the establishment of stable interactions between pests and natural enemies in grain crops (13, 16, 25).

It is perhaps for these reasons that the microbial pesticide approach using fast-acting pathogens has received more research attention than any other biological control approach to pest suppression in grain and row crops. The bacterium *Bacillus thuringiensis*, which produces compounds that are quickly toxic to some insects, can be used effectively in this manner. The microbial pesticide approach is also being taken to develop fungi that control weeds (10, 16).

The conservation approach has received the least research attention. Little incentive exists for the private sector to develop these technologies because the product that is developed is management information. Successful development of this approach will most likely fall to public sector researchers. Methods to control communities of organisms in a systemic fashion rather than a single control agent are needed (11).

Research Needs

Extensive research in many disciplines will be required if biological control is to become more widely used. A better fundamental understanding of pest-natural enemy interactions, ecology, and population biology is needed, as well as attention to more applied problems of mass rearing, formulation, and delivery required to make these control agents commercially viable. Successful development will require a multidisciplinary approach and will draw from expertise in many fields, including: systematic (taxonomy), ecology, behavioral science, physiology, genetics, chemistry, and epizootiology (the study of population disease at the population level), among others (10, 16, 25, 38).

Taxonomic, biochemical. and genetic comparisons of pests from the same or similar species taken from geographic areas of suspected evolutionary origin also are needed. These studies can help identify pests and their natural enemies, improve understanding of the relationship between pest and enemy, and determine the geographic distribution of each. Use of classical biological control methods will be enhanced if techniques can be developed to detect and eliminate parasites and pathogens from the imported natural enemy cultures (10, 16, 25, 38).

An improved understanding of the natural enemy-pest dynamics and factors that enhance the effectiveness of control is needed. Elucidation of the structure and roles of insect hormones and compounds that attract or repel pests is needed. Additional research is needed to understand the natural enemy population (i. e., infectivity, virulence, specificity of host; biological fitness including survival, persistence, and dispersal; the role of population density, etc.), the pest population (i.e., susceptibility, development of resistance, mechanisms of immunity, population density impacts, and distribution), the effects of the abiotic and biotic environment (i. e., weather, soils, host plants, biotic transport agents, sunlight, cropping patterns, etc.), and the environmental impacts of releasing predators, parasites, and pathogens to control pests (10, 16, 25, 38).

A major constraint to using the augmentation approach to biological control is the inability to cost-effectively

[10] Recent work With baculoviruses to control insects has been promising and this biological control agent may prove to be an exception to this statement (16).

raise large numbers of parasites, predators, and pathogens. The life cycles of many natural enemies are complex and raising these organisms in an artificial setting is difficult. New mass rearing techniques need to be developed for many biological control agents.

For natural enemies that are parasitic insects, laboratory rearing requires maintaining not only the host insect, but the food source of the host insect as well, which may include plants that are themselves difficult to grow. Thus, mass rearing of a parasitic insect requires maintaining both an appropriate plant population and host insect population, a costly arrangement that points to the need to develop artificial diets (10, 25).

Viruses can also be difficult to mass produce. Viruses are obligate cellular parasites and must be produced within living cells. For viruses that are pathogenic to insects, this can be accomplished either by infecting whole insects or by infecting cultures of continuous cell lines derived from the host insect. Recent advances in insect cell culture is improving the prospects of virus pesticide production. Significantly, most of these advances are being made in the biomedical field rather than the agricultural field, because biomedical industries are using certain classes of viruses (such as baculoviruses) as vectors to express foreign genes for high-level production of biological and pharmaceutical products (16).

Mass production techniques for fungal spores are also needed. The application of automated systems and robotics to mass production could potentially significantly reduce the cost. Other problems encountered while mass rearing natural enemies include the loss of genetic variability and the loss of effectiveness of species that have been raised for several generations in the laboratory (16, 25).

The performance of biopesticides in the field has often been highly variable due to environmental factors, interactions with other organisms, and poor delivery to target organism among other problems. Formulation of biopesticides (mixing of the cultured microbial preparation with inert agents to achieve proper dilution, deposition, moisture holding capacity, protection from ultraviolet rays, shelf life, slow release, etc.) must be improved to increase efficacy in the field. Long-range needs include identifying new control agents, increasing the toxicity of agents against susceptible pests, and expanding the range of hosts of the control agent (10, 16).

Delivery systems also need to be improved. Techniques must be designed to promote maximum efficacy and ease of application. New sprayer technologies, application of biopesticides by irrigation methods, and timed release formulations are needed.

Finally, a general need exists to assess the efficacy and impacts of control agents after release. Studies using biological control agents have rarely adequately documented efficacy, reliability, and economic feasibility. Population establishment and buildup, degree and timing of feeding damage, plant population density and productivity, plant stress, and nontarget side effects need to be assessed. Any changes in the fitness of the naturalized bioagent need to be ascertained to ensure efficacy and environmental safety. While these questions are pertinent to all biological control agents, they will be critical to regulatory approval of genetically engineered control agents (10, 16, 25, 38).

Use of Biotechnology in Biocontrol Research

Traditional technologies, such as chemical- or ultraviolet-generated mutations followed by selection for desired phenotypic traits, and sexual mating will continue to play a role in producing and identifying natural enemies via improved control capability or host range. Additionally, traditional culture techniques can be used to induce increased secretion of certain toxins and enzymes involved in pathogenesis. However, new biotechnology tools, such as protoplasm fusion and gene transfer, will also be used to improve virulence, sporulation, fitness for survival, infectivity under suboptimal conditions, and production of pesticidal metabolizes; and to expand host range and the tolerance of control agents to certain chemical pesticides (10, 16, 25, 38).

Biotechnology to improve biological control agents, such as insects and other arthropods, nematodes, protozoans, and fungi, is technologically more complex than biotechnology involving viral and bacterial control agents. Use of genetic engineering in predator and parasitic insects is constrained by the lack of universal vectors or other techniques to transfer foreign genes into the insect, and the lack of useful insect genes that have been cloned. Recombinant DNA techniques are being used to turn slow acting viruses into quick acting viruses, and to increase virus virulence. Genetic engineering is being used to improve the delivery of *Bacillus thuringiensis* toxin to the pest. Methods include incorporating the toxin gene into bacteria that inhabit seed coatings, roots, or surface films where target insects feed. Genetic engineering in fungi is being used to improve germination, penetration of the insect cuticle, and increase toxicity. Little biotechnology research has been conducted using protozoans and nematodes (10, 16, 25, 38). In addition to enhancing the field efficacy of biological control agents, biotech-

nology provides powerful research tools to further our basic understanding of the physiology and biology of these control agents and their environment.

Institutions Involved in Biological Control Research

Biological control research has been conducted primarily by public sector institutions, such as the U.S. Department of Agriculture (i.e., the Agricultural Research Service, the Office of International Cooperation and Development, the International Research Division, and the Forest Service), the Land Grant University System, and other public and private universities. Other Federal agencies that have supported biological control research include the U.S. Army Corps of Engineers (primarily for aquatic weeds), the Department of Interior (mainly the Park Service), the Department of Energy (through the national laboratory system), and the Tennessee Valley Authority. Selected State Natural Resources or Agricultural departments (notably those of California and Florida) also have supported biological control development. The U.S. Environmental Protection Agency is involved in registering biological control agents as pesticides. The U.S. Department of Agriculture Animal and Plant Health Inspection Service regulates the importation of natural enemies and the environmental release of biological control agents. The State Department also is involved in obtaining permission to search foreign countries for natural enemies of pests imported to the United States, and with negotiating release conditions of natural enemies with Canada and Mexico (10, 16, 25, 38).

Private industry interest has been focused primarily on organisms that can be used in microbial pesticide applications, such as *Bacillus thuringiensis* to control insects, and a few selected fungi (i. e., CASST, COLLEGO, and DeVine) to control weeds. A limited level of private-industry support exists for the use of predators and parasites to control arthropods. A few small, private firms mass rear parasites and predators for release, but conduct little or no research (10, 16, 25, 38).

Use of Biological Control Agents To Control Pests in the United States

Biological Control of Arthropods: Parasites and Predators

Arthropod (e.g., insects, spiders, mites) damage is a major contributor to crop losses and decreased quality of agricultural products. A wide array of biological control agents can be used to control arthropods, bacteria, viruses, fungi, protozoa, and nematodes. In the United States, these agents have been used to control several arthropod species (table 2-6). The classical method of control is the approach used most often, and the greatest success has occurred in more stable habitats such as forests and orchards, rather than row crops.

Table 2-6—Use of Parasite or Predator Insects To Control Insect Pests in the United States

Pest insect	Host plant
Classical method	
Rhodesgrass scale	Grasses
Citrus blackfly	Citrus
Walnut aphid	Walnuts
Cottony cushion scale	Citrus
Olive scale	Olives
Spotted alfalfa aphid	Alfalfa
Alfalfa weevil	Alfalfa
California red scale	Citrus
California purple scale	Citrus
California yellow scale	Citrus
Browntail moth	Forests
Satin moth	Forests
Oriental moth	Forests
Elm leaf beetle	Forests
European pine sawfly	Forests
European spruce sawfly	Forests
Larch casebearer	Forests
Larch sawfly	Forests
Augmentation method	
Mexican bean beetle	Soybeans
Mealybugs	California citrus
California red scale	Citrus
Spider mites	Almonds
Two spotted spider mite	Strawberries
Conservation method	
European red mite	Apples

SOURCE: Office of Technology Assessment, 1992.

Traditional selection methodologies have been used to identify parasites or predators with improved control capability or host range. For example, such techniques were used to identify strains of a parasitic mite resistant to selected pesticides, which were subsequently released into California almond orchards to control spider mites. Increased pesticide resistance allows this parasitic mite to be used in conjunction with Integrated Pest Management programs that use pesticides to control navel orangeworms above a threshold level. The ability to use this predatory mite in conjunction with other insect control programs increased the acceptance of this parasite for spider mite control (25).

Use of genetic engineering in predator and parasitic arthropods is constrained by the lack of universal vectors or other techniques to transfer foreign genes into the arthropod. Current research is focusing on the use of transposons to transfer genes, but transposons may be

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

The parasitic wasp *Microplitis croceipes* lays her eggs in the tobacco budworm. By putting this natural predator to work, scientists hope to control members of the genus *Heliothis*, which cause major damage to cotton, corn, soybeans, and other crops.

specific to certain species of insects, and thus cannot be used as a universal mechanism to transfer genes to all insect species. Another major constraint is the lack of **useful** arthropod genes that have been cloned (25).

Further development of predator and parasitic arthropods to control pest arthropods is being constrained by several factors. Selection standards for classical control approaches are needed. The economic importance of the target pest is frequently the only factor considered when selecting possible subjects for biological control. Characteristics of the natural enemy itself, such as its suitability of mass rearing at reasonable cost, additional host requirements, impact on beneficial or endangered species, or dispersal characteristics may not be considered (25).

Use of augmentation techniques to control pest arthropods with other parasitic and predator arthropods is limited by the lack of artificial diets and subsequent high cost of mass rearing, incomplete information on release methods, lack of rapid and effective monitoring methods, and lack of ability to stockpile or store natural enemies or maintain gene banks. Quality control standards for private firms that mass rear predatory or parasitic arthropods are lacking. Mixed colonies or even colonies of the wrong species have sometimes been provided; in some cases, firms have produced parasitic arthropods unable to fly. Arthropods can be sold without guidelines as to number to release, optimal timing of release, or how to monitor efficacy of release. Professional quality standards and appropriate management information are needed (25). Conservation methods to maintain predator or parasitic arthropods are constrained by gaps in the knowledge of the role of natural enemies in crop systems and how best to modify management practices to maintain natural populations.

Table 2-7—Pathogens Used To Control Insects in the United States

Pest insect	Host plant
Viruses	
European pine sawfly	Trees
Douglas fir tussock moth	Trees
Soybean looper	Soybeans
Velvetbean caterpillar moth	Soybeans
Gypsy moth	Trees
Bacteria	
Japanese beetle	Turf grass
Mosquito larvae	NA
Greater wax moth	Beehives
Fungi	
Browntail moth	Trees
Plant bug	Apples
Aphids	Potatoes
Spotted alfalfa aphid	Alfalfa
Mosquito larvae	NA
San Jose scale	Trees
Whiteflies	Trees
Protozoa	
Grasshoppers	Rangeland
European corn borer	Corn
Nematodes	
Butterflies, beetles	Cranberry, Citrus
Face fly	Cattle
Mosquito larvae	NA

NA = Not applicable,

SOURCE: Office of Technology Assessment, 1992.

Biological Control of Arthropods: Pathogens

In addition to parasitic and predatory arthropods, pathogens can be used to control pest arthropods. Pathogens that have been used to at least partially control arthropods (almost exclusively insects) in the United States include bacteria, particularly different strains in the *Bacillus genus*; viruses, particularly members of the baculovirus group; fungi; protozoans; and nematodes (table 2-7). *Bacillus thuringienses* (Bt), discussed earlier, is the pathogenic bacteria most frequently used to control insects.

The tools of biotechnology can be used to improve the delivery of the Bt toxin to insect pests. The gene that codes for the toxin can be incorporated into bacteria other than *Bacillus thuringiensis;* these bacteria may inhabit seed coatings, roots, or surface films where target insects feed. Genes coding for Bt toxins have incorporated in strains of *Pseudomonas,* a soil bacteria that colonize corn roots, and into *Clavibacter xyli,* a plant-associated (endophytic) bacterium that grows in the vascular tissues of

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Entomologist compares an insect ravaged cotton leaf from a control variety with one that has been genetically engineered with a protective gene from *Bacillus thuringiensus.*

plants. The Monsanto and Mycogen Corp. are incorporating Bt toxin genes into *Pseudomonas,* while Crop Genetic International is working with *Clavibacter (1,* 16).

Genetic engineering techniques are also being used to modify Bt toxin genes to be toxic to a broader range of pests and to be more potent. Traditional selection and screening procedures applied to natural isolates are being used as well, to identify strains of *Bacillus* bacteria that are either more efficacious or that have different host specificity. These methods will potentially extend Bt use to include control of cotton bollworm, European corn borer, and corn rootworms. Genetically engineered and new, naturally selected strains of Bt are expected to be commercially available by 1995 (1, 16).

Viruses are also being used to control insects. Many types of viruses infect insects, but only a few cause pathogenic epizootic diseases that are sufficiently fast-acting and widespread to be considered useful for pest control. The first virus to be registered by EPA and produced commercially as a pesticide was a type of baculovirus that forms large polyhedral occlusions within the nucleus of infected cells. It was marketed in the mid 1970s by the Sandoz Corp. under the name Elcar, and was used to control cotton bollworm. Its market was displaced by the new pyrethroid pesticides. It has not been remarketed, although increasing resistance to pyrethroids may lead to renewed commercial interest. Three other baculoviruses have been used by the U.S. Forest Service to control the Douglas fir tussock moth, the gypsy moth, and the European pine sawfly (16).

Baculoviruses are used to control lepidopterans (butterflies and moths) because they cause widespread lethal epizootic diseases, lead to morbidity within a week of infection, are compatible with other agrichemicals, can be applied by conventional spraying techniques, and are stable on the shelf for extended periods of time (years). Further, the baculoviruses replicate only in arthropods. Each is specific to a host or group of closely related hosts, and must enter and replicate within a specific type of host cell. This specificity is attractive from an environmental control perspective (1).

Two other viruses of potential usefulness for biological control of insects are the *Autograph californica virus* and the codling moth granulosis virus. *A. californica* has a relatively wide range of hosts and could be used to control alfalfa looper, cabbage looper, fally armyworm, beet armyworm, and wax moth. The codling moth granulosis virus could be used to control insects that affect pome fruits and walnuts (16).

Genetic engineering is being used to make viral pesticides faster acting. Neurotoxin genes that paralyze the pest insect and quickly halt insect feeding are being introduced into baculovirus. Alternatively, insecticidal hormones can be incorporated into the baculovirus to disturb insect development or behavior. The genes that code for an enzyme that regulates juvenile hormone levels in insects; a protein that regulates the release of a major molting hormone; and a protein hormone that elicits several behavioral characteristics during molting all recently have been isolated (1).

The lack of suitable cloned neurotoxins and insect hormone genes is delaying further progress in improving viral control agents. Promotors that can be recognized by selected host cells of pest insects (i.e., cells of the midgut, for example) are being used to extend baculovirus ranges. The recent discovery that baculoviruses normally contain a gene regulating insect molting hormone activity is leading to the development of baculovirus strains in which this gene has been deleted. These gene-deleted strains have been shown to reduce insect feeding during infection, and to hasten the onset of insect morbidity (1).

Baculoviruses genetically modified to delete the insect molting hormone regulatory gene are expected to be available before 1995. Baculoviruses engineered to carry

Table 2-8—Control of Weeds by Insect and Microbial Agents in the United States

Weed	Habitat/crop affected
Alligator weed	Aquatic
Lantana	Rangeland, forest, crops
Musk thistle	Rangeland
Northern jointvetch	Rice and soybeans
Persimmon	Rangeland
Prickly pear cactus	Rangeland
Puncture vine	Pasture, annual crops
Skeletonweed	Rangeland
St. Johnswort	Range and arable lands
Stranglervine	Citrus
Water hyacinth	Aquatic

SOURCE: Office of Technology Assessment, 1992.

insecticidal genes such as insect hormones and neurotoxins could be available in the late 1990s.

The only fungus registered and commercially produced for insect control in the United States was *Hirsutella thompsonii.* This fungus was used to control citrus rust mites, **but** was not commercially successful primarily **because it did** not survive storage or transportation. Further, environmental factors, including insufficient moisture, adversely affected its efficacy. Genetic engineering of fungi is now being used to improve germination, improve penetration of the insect cuticle, and increase toxicity (16).

A major limitation to using protozoans is that they kill insects very slowly, if at all. Generally they affect arthropods by causing chronic disease with sublethal effects, reducing the ability of the arthropod to survive the winter. *Nosema locustae,* used to control grasshoppers on rangeland, is the only protozoan to be registered and commercially available in the United States (16).

Research involving nematodes has been increasing. *Steinernema carpocapsae* has been used in the United States to control some lepidoptera species. It is not effective if applied to vegetation surfaces or other situations where it can dry out, but it can be effective in the soil or in burrows in plant tissues. *Dedalenus siricidicola* has been used to control woodwasps, even though its action is to sterilize its host rather than kill it. Very little genetic engineering is being used with nematodes.

Biological Control of Weeds: Microorganisms and Arthropods

Historically, biological control of weeds most commonly has been mediated by microorganisms (mainly bacteria and fungi, see table 2-8) and insects. Worldwide, 89 species of weeds have been controlled using 192 species of introduced organisms (the classical approach); an additional 25 weed species have been controlled using 33 species of native organisms (the bioherbicide approach) (10).

Pathogenic microorganisms kill or severely debilitate their host plants by causing disease. Pathogenic and nonpathogenic microbes also produce metabolizes that are toxic to plants, and these phytotoxins can also be used as herbicides. For example, the fungus *Gliocladium virens,* when prepared and applied properly, can release enough of the toxin viridiol in the soil to control pigweed without harming cotton seedlings.

The private sector has shown interest in developing microbial herbicides. Two microbial herbicides (COLLEGO and DeVine) are commercially available and four others are undergoing trials for registration as herbicides (table 2-9). Other microbial herbicide candidates are undergoing experimental development. About 107 fungi and 1 bacterium are being evaluated worldwide as bioherbicides (10). Additionally, a parasitic nematode, *Orrina phyllobia,* has been shown to be a practical means to control silverleaf nightshade.

Development of a microbial herbicide can take several years. For example, it is estimated that the development of COLLEGO® took 11 years of effort from the time of discovery to commercial availability at a cost of about $1 to $1.5 million. In comparison, a typical chemical herbicide takes 7 to 10 years to develop and costs approximately $80 million. Early research on microbial herbicides is subsidized by public funds, but the expense of large-scale fermentation, toxicology testing, formulation, and registration are borne by industry. In some cases, these costs could prove to be quite high (10). Further development of microbial herbicides will require improved mass production, formulation, and delivery systems. Some native pathogens, such as the rusts and certain smut fungi, cannot be artificially grown. Methods to obtain sufficient quantities of these pathogens from infected plants must be developed.

Weed pathogens are being genetically manipulated to improve virulence, sporulation, fitness for survival and infection under suboptimal conditions, and production of herbicidal metabolizes; to expand host-range; and to increase tolerance to certain chemical pesticides. For example, it has been discovered that altering a single enzyme *(pisatin demethylase)* **can** cause a fungal pathogen, but not a nonpathogenic fungi, to become virulent on new host plants. Genetic engineering techniques are also being used to increase virulence by transferring genes encoding herbicidal phytotoxins to pathogenic microorganisms (10).

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Table 2-9—Microbial Herbicides Commercially Available or in Development in the United States

Herbicide	Pest	Crop/habitat effected
COLLEGO®	Northern jointvetch	Rice
DeVine®	Stranglervine	Citrus
CASST™[a]	Sicklepod	Soybean and peanut
BioMal™[a]	Round-leaf mallow	Annual crops
Cercospora rodmanii[a]	Waterhyacinth	Aquatic
Mycoleptodiscus terrestris[a]	Eurasian watermilfoil	Aquatic

[a]Undergoing trials

SOURCE: Office of Technology Assessment, 1992.

Table 2-10—Use of Insects To Control Weeds in the United States

Weed	Crop/habitat affected
Classical approach	
St. Johnswort	Range and arable lands
Lantana	Rangelands, forests, and plantation crops
Alligatorweed	Aquatic
Prickly pear cactus	Rangeland
Puncturevine	Pastures and annual crops
Tansy ragwort	Rangeland
Hydrilla	Aquatic
Purple loosestrife	Range and arable lands
Leafy spurge	Rangeland
Diffuse, spotted and Russian knapweeds	Rangeland
Yellow starthistle	Rangeland
Salt cedar	Rangeland and forests
Field bindweed	Various crops
Waterlettuce	Aquatic
Broom snakeweed	Rangeland
Baccharis neglecta	Range and arable lands
Augmentation approach	
Waterlettuce	Tried and discontinued
Purple nutsedqe	Tried and discontinued

SOURCE: Office of Technology Assessment, 1992.

Traditional techniques are also used to alter pathogen characteristics. These include chemical- or ultraviolet-generated mutations followed by selection for desired phenotypic traits, breeding, and nonsexual transfer of hereditary properties. Cultural techniques also are being improved to increase secretion of certain toxins and enzymes involved in pathogenesis.

In addition to microbial pathogens, insects and other arthropods also can be used as biological control agents for weed control (table 2-10). The relationship between insects and weeds is complex. Some weeds (e. g., St. Johnswort) can be controlled with just one insect. Others may require more than one insect for control. For example, control of tansy ragwort, a poisonous weed found in the Pacific Northwest, is mediated by a moth that defoliates it and a second insect that feeds on its root as a larva and on the resprouting growth as an adult. This relationship between each co-evolved arthropod and its weed host makes each study unique and raises the question of whether scientific expertise will ever be adequate to fully assess the potential for weed control by arthropods (10).

Arthropod adults and immature larva and nymphs feed and complete at least a part of their life cycles on certain weeds. In this process, they damage the plants, weakening and reducing their productivity and competitiveness. In general, the feeding activity of immature arthropods is more damaging than that of adult arthropods. The extent of the damage caused by arthropod feeding depends on the particular weed tissues destroyed, the timing of the damage as it relates to the plant's growth cycle, and the extent of other plant stresses present. For example, sucking insects and grasshoppers defoliate plants late in the plant's life cycle and do not cause as much damage as insects that defoliate plants early in their life cycles. Arthropods that attack the seeds of weeds that cannot reproduce vegetatively are likely to have the greatest impact on weed control. In addition to feeding damage, some arthropods weaken plants by introducing toxins causing cell proliferation and gall formation (10).

Of the more than 250 naturalized plant species considered to be major weeds, only a few dozen have been considered for classical biocontrol by arthropods. Nonetheless, this approach has been the most common and successfully used method of biological weed control. It is estimated that the control of St. Johnswort by insects has yielded benefits worth approximately $2 million per year. It takes 1 to 4 years to find and clear each insect or other arthropod biocontrol candidate and development costs are estimated at $1 to 2 million. However, the estimated return on research is about $30 for every $1 invested (10). Few attempts to control weeds with ar-

Photo credit: U.S. Department of Agriculture, Agricltural Research Service.

Tiny (1/8th inch long) flea beetle, *Apthona flava,* on leafy spurge is one of several biological control agents tested to combat a costly weed that infests 2½ million acres of rangeland in the Great Plains.

thropods using the augmentation approach have been tried, and generally they have been discontinued.

Traditional selection methods are used to select cold-tolerant strains of weed-damaging insects and strains whose larva have higher survival rates in hot weather, and whose prediapause behavior has been altered. Genetic engineering is not currently used to improve arthropods as biological control agents (10).

Biological Control of Disease

Biological control of plant diseases is achieved by decreasing pathogen populations or by preventing the occurrence of infections. Approaches taken include manipulating resident microbial communities to decrease disease (conservation approach) or applying to the plant organisms antagonistic to pathogens (augmentation). Only three plant disease biocontrol agents are commercially available (table 2-11) (38).

Table 2-1 l—Biological Control Agents Commercially Available To Control Plant Disease in the United States

Agent	Disease controlled
Bacteria	
Agrobacteriurn radiobacter (strain K84)	Crown gall in dicots
Pseudomonas fluorescent.	Damping off and root rot in cotton
Fungi	
Peniophora gigantea.	Root and butt rot in conifers

SOURCE: Office of Technology Assessment, 1992,

Use of *Agrobacterium radiobacter* to control crown gall in dicots costs an estimated 1 to 5 cents per plant treated, and less if the seeds are treated. *Peniophora giganted* applied to freshly cut conifer stumps preempts colonization by the pathogen responsible for root and butt rot, diseases resulting in annual losses of nearly $1 billion. *Pseudomonas j7uore.seen.s,* sold under the name of Dagger G by Ecogen, controls diseases in cotton. In 1989, it was used on approximately 75,000 acres of cotton in the Mississippi Delta region (38).

Diseases that potentially could be controlled in the next decade include take-all disease in wheat, and damping-off and root rot in crops other than cotton. Yeasts to suppress *Penicilliurm* and other postharvest pathogens in citrus and other fruit; the bacterium *Bacillus subtilis* to control brown rot in peaches; and compost amended potting media to control *Rhizoctonia* and *Pythium* in nursery stocks are other potential control agents (38).

The use of microbial disease control agents has been plagued by inconsistent efficacy in the field. In some cases, agents that have worked in one field have failed to be effective in immediately adjacent fields. The biocontrol agent and pathogen interact in the midst of a vast array of other microorganisms that sometimes decrease the efficacy of the control agent *(23, 24).* A better understanding of the community dynamics, population and community ecology, population genetics of plant-associated microorganisms and of the mechanisms that regulate the community structure and dynamics of plant-associated microorganisms is needed.

Much of the research in the area of biocontrol of plant diseases has focused on improving the understanding of the mechanisms by which biocontrol agents prevent disease. One mechanism of action called interference competition or antibiosis refers to the inhibition of one organism by a metabolic product of another. The use of the bac-

terium *Agrobacterium radiobacter* strain K84 to control crown gall tumors caused by *Agrobacteriurm tumefaciens* is an example of this type of mechanism. *A. radiobacter* produces an antibiotic to *A. tumefaciens.* Control of take-all disease in wheat by ***Pseudomonas fluorescens*** strain 2-79 is another example of antibiosis (38).

Peniophora gigantea controls root rot in pine caused by the fungus *Heterobasidion annosum,* on the other hand, by competing with the fungus for nutrients and space, a process referred to as exploitation competition. A third mechanism, hyperparasitism, occurs when fungal pathogens destructively parasitize another organism. **Fungi of the** *Trichoderma* and *Gliocladium* family, for example, parasitize soil-born plant pathogens such as *Rhizoctonia solani and Pythium* species. A fourth mechanism of disease prevention by biological agents is hypovirulence. For example, some strains of the chestnut blight fungal pathogen *Cryphonectria parasitic* (those with reduced virulence) can impart protection to chestnut trees from more virulent strains of this pathogen.

Traditional screening techniques are being used to develop fungicide-resistant strains of the fungus *Trichoderma,* which allows this disease control agent to be used with fungicides so that fewer chemicals need be applied. Strains of the bacteria *Pseudomonas syringae* pv. tomato, which controls bacterial speck in tomatoes, have been made resistant to copper. The copper resistance allows *P. syringae* to be used in the presence of copper bactericide. Combinations of *P. syringae* and copper bactericide gives greater control over bacterial disease than occurs with the biocontrol agent or bactericide treatment alone (31, 32).

Pathogenic organisms can become resistant to biological control agents. For example, *A.* ***radiobacter*** controls the plant pathogen *A. tumefaciens* **by** producing a compound called agrocin. The gene producing agrocin is carried on a plasmid, which can be naturally transferred to *A. tumefaciens.* Thus, *A. fumefaciens is* becoming resistant to *A. radiobacter.* Genetic engineering is being used to construct mutant strains of *A. radiobacter* that no longer have the ability to transfer the agrocin plasmid, thus decreasing the potential of *A. tumefaciens* to develop resistance to this natural pesticide. Protoplasm fusion techniques are also being used to construct strains of *Trichoderma harzianum* that are more effective than parental strains in controlling *Pythium ultimum (38).*

Biological Control of Frost Damage

The temperature at which frost injury occurs in a number of crops is determined by the population density of ice-nucleation-active bacteria on plant leaves. By decreasing the numbers of these bacteria, some protection against frost damage can be achieved. The application of non-ice-nucleating bacteria prior to colonization of ice-nucleating bacteria can effectively prevent the establishment of the ice-nucleating bacteria by limiting the resources (i.e., space and/or nutrients) available to the ice-nucleating bacteria. Ice-minus deletion mutants of the bacteria *Pseudomonas syringae* have been constructed to control frost. The first planned introductions of genetically engineered bacteria into the environment in the United States involved the field-testing of these ice-minus bacteria.

SUMMARY

Pest control is a major concern of crop producers in the United States. Each year, pest damage results in billions of dollars of lost revenue to farmers. Poor weather conditions add to those losses. To control pest damage, farmers have traditionally used chemical approaches. Biotechnology is now providing opportunities to use biological approaches such as transgenic plants resistant to pests and better adapted to geoclimatic conditions, and the use of biological control agents.

The ability to create transgenic plants with useful agronomic characteristics is constrained by the lack of knowledge concerning plant physiology. Our understanding of plant metabolism has not kept up with the development of biotechnology methods. However, plants resistant to certain insects are approaching commercialization. Most of these plants have a *Bacillus thuringiensis* toxin gene insert, **but** some research also is being conducted using insect trypsin inhibitors that disrupt the digestion of feeding insects. Several transgenic Bt plants are undergoing field trials, and it is expected that several companies will begin petitioning EPA for approval for commercial release soon.

Plants tolerant of herbicides are being developed to aid the management of weeds. Development of broad-spectrum herbicides has been constrained because they not only kill most weeds, but also cause significant damage to crops. Crops tolerant to specific herbicides allow the use of these herbicides in conditions where they previously could not be used, and may allow for the replacement of some environmentally damaging herbicides. Some of these crops are nearing commercialization stages.

Transgenic plants are being developed that are resistant to disease. Scientific understanding of the complex interactions between fungi or bacteria and host plants is limited, so much of the early successes have been in

developing plants resistant to certain viral diseases. Several virus-resistant plants are under development.

Development of transgenic plants tolerant to geoclimatic conditions is in the early stages. Research is being conducted to understand the mechanisms of heat and drought tolerance, and to enhance the ability of plants to withstand cold temperatures. However, the successful commercialization of these plants is unlikely to occur before the end of the decade.

In addition to engineering crops themselves, there is increased interest in developing biological control agents to manage pests. The use of biological control in the United States, to date, is relatively limited and most successes have involved controlling pests in forests, orchards, grasslands and aquatic environments. Use of biological control in grain and row crops is very limited. However, there is more emphasis placed on developing such products to control weeds, insects, and disease in the major food crops, and improved strains of *Bacillus thuringiensis* to control insects and a few fungal strains to control weeds are approaching commercialization. More research still is needed to successfully develop other products.

The food processing industry will also be affected by biotechnology. Plants are modified for new quality and processing characteristics. For instance, tomatoes with delayed softening characteristics are nearing commercialization. Research is also underway to alter the starch, oil, and protein content of selected crops to more closely reflect consumer preferences and to enhance their processing characteristics for specific end uses. Diagnostic kits are in various stages of development to detect the presence of microorganisms, chemicals, and other contaminants in food products.

The development of transgenic plants and biological control organisms offer new approaches to controlling pests and to improving food processing characteristics. However, many issues have been raised concering the development of these products. Some groups are worried about the effects these products will have on small farms, and on food safety and the environment. Additionally, many of these products will require extensive farm management capabilities for effective use. These issues will be discussed in subsequent chapters.

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Chapter 3

Emerging Animal Technologies

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Chapter 3
Emerging Animal Technologies

The U.S. livestock industry is immense, and the costs of running it are correspondingly large. Feed and health care costs for the Nation's nearly 100 million head of cattle (beef and dairy), 55 million pigs, 10 million sheep, and 600 million chickens and turkeys amount to billions of dollars annually. Disease and reproductive losses also significantly erode industry profits.

Like any industry, livestock producers strive to reduce costs and losses, and to maximize profits. Feed constitutes almost 70 percent of the cost of producing pigs for pork. Improvements in feed efficiency (i.e., a lower quantity of feed consumed per unit of weight gained) and faster weight gain could potentially lower production costs in this and other sectors of the livestock industry. Animal diseases cost the livestock industry billions of dollars each year. For example, anaplasmosis in cows costs an estimated $300 million a year in losses and disease control. The bacterium *Staphylococcus aureus*, which causes 55 percent of mastitis, costs U.S. dairy producers some $250 million annually. New vaccines and diagnostic kits can help decrease disease in livestock. Other economic losses in the livestock industry result from low conception rates and embryo mortality. Such losses can be minimized by a greater understanding of reproduction as well as by emerging technologies for improving reproductive success.

Biotechnology has the potential to improve feed efficiency, reduce losses from disease, and increase reproductive success in all sectors of the livestock industry, in part by furthering our understanding of animal physiology, and in part through the development and commercialization of new techniques and products.

The term biotechnology refers to a wide array of techniques that use "living organisms (or parts of organisms) to make or modify products, to improve plants or animals, or to develop microorganisms for specific uses' (45). Under this broad definition, biotechnology includes many long-practiced technologies, such as animal breeding and cheese, wine, and beer making. Generally, however, the term biotechnology is used in reference to such new technologies as recombinant DNA techniques (also called genetic engineering), cell culture, and monoclinal antibody (hybridoma) methods. The application of these new methods to the livestock industry has already generated a number of products for improving production, animal health, and food processing, and will continue to do so.

Biotechnology is specifically used to produce products that will promote growth and increase feed efficiency and carcass leanness in growing animals, and significantly increase milk production in lactating animals. New reproductive technologies are providing means to rapidly upgrade herd quality. Transgenic animals are being produced to grow faster, have greater disease resistance, and to produce high-value pharmaceutical products. New vaccines and diagnostic kits are being developed to improve livestock health. Biotechnology is also being used to process meat and dairy products and to detect food contaminants that might be present in those products. This chapter presents some new livestock biotechnologies currently under development. [1]

COMPOUNDS THAT PROMOTE GROWTH, ENHANCE FEED EFFICIENCY, AND REDUCE CARCASS FAT

Compounds currently used in the livestock sector to promote growth and increase feed efficiency, such as anabolic steroids and antimicrobial compounds, will continue to be used. However, new products are also being developed, including protein hormones called somatotropins and catecholamine compounds called beta-adrenergic agents. These compounds increase growth rates in young animals, improve the efficiency with which food is converted to muscle, and significantly reduce carcass fat so that meat products are leaner. Somatotropins also increase milk production in lactating dairy cows. Currently, recombinantly-derived bovine and porcine somatotropins are undergoing Food and Drug Administration (FDA) review for use in lactating dairy cows and pigs, respectively, and one beta-adrenergic agent is undergoing testing for approval in pigs.

[1] Because of the large quantity of research on these technologies, this chapter will mainly cite OTA **commissioned background** papers and other review articles.

Somatotropin

A hormone is a chemical that is produced by one organ or cell and transported to another to cause a biological effect (i. e., it is a chemical messenger between different cells and organs of the body). Hormones can be steroids, proteins, peptides, or modified amino or fatty acids. About 70 percent of the hormones in blood are protein hormones. Somatotropin is a protein hormone produced by the pituitary gland, a small gland located at the base of the brain. All vertebrates (i.e., animals that have backbones) produce somatotropin. In addition, evidence exists that some nonvertebrate animals, such as shellfish (i.e., oysters, clams, etc.), also produce somatotropin.

All major livestock species produce somatotropins unique to each species. Naturally produced bovine somatotropin (bST) **contains 190 or 191 amino acids, and** each polypeptide can contain either the amino acid valine or leucine at position 126, which gives rise to 4 variants of bST. Pigs produce porcine somatotropin (pST) consisting of 191 amino acids. The amino acid sequence of pST, however, differs from bST at 18 positions. In contrast, bST and ovine (sheep) somatotropin (oST) differ by only one amino acid position (3, 16, 40).

Differences in the amino acid sequence of proteins lead to species specificity. The amino acid sequence determines the unique three-dimensional shape characteristic of a specific protein. Only proteins of the appropriate shape bind to a receptor, and thus elicit a biological response. Proteins from one species that differ by many amino acids from the equivalent protein in another species generally do not elicit a biological response in the other species. Conversely, bST and oST that differ only by one amino acid are active in either sheep or cattle. However, human somatotropin differs from pST by 59 amino acids and from bST by 68 amino acids (a 35 percent difference). Bovine, porcine, and ovine somatotropin are not biologically active in humans (20, 23, 49).

Mechanism of Action

Somatotropins affect growth rate, feed efficiency, milk yield, and the proportion of fat and protein in the carcass. These effects occur in response to the coordination of numerous metabolic pathways by somatotropin. These metabolic effects are both direct and indirect. The direct effects include nutrient partitioning among tissues, most specifically liver and adipose (fat) tissue (table 3-1). indirect effects include those mediated by insulin-like growth factor-1 (IGF-I), whose secretion is stimulated by somatotropin.

Somatotropin affects glucose metabolism. Glucose is a carbohydrate used as an energy source by many tissues, or as a raw material for the synthesis of other molecules (as in the production of milk lactose). Administration of somatotropin increases blood glucose levels by stimulating glucose production by the liver, and may possibly reduce glucose use for energy by other body tissues.[2] Thus, additional glucose is available for uses such as increased growth or milk production while normal body functions are still maintained. The changes in glucose use by body tissues and glucose production by the liver appear to be caused by somatotropin altering the response of these tissues to acute signals, such as to insulin and other hormones that affect glucose metabolism (3. 16).

Somatotropin also adjusts lipid (fat) metabolism. In growing pigs, for example, somatotropin redirects nutrients (primarily glucose) away from fat synthesis to providing energy for lean tissue accretion. The adjustments in tissue lipid metabolism depends on the nutritional status of the animal. If an animal's energy (food) intake is greater than its requirements, somatotropin allows for the reallocation of nutrients to support increased lean tissue accretion (growth) or milk production (lactation) instead of storing excess nutrients as body fat. If the animal's nutrient intake is equal to or less than its requirements, somatotropin directs adipose tissue to mobilize deposits of body fat so that these energy reserves can be used to support the increased lean tissue accretion (growth) or milk production (lactation). The former situation is more likely to be the case for young growing animals and the latter situation would be typical of lactating cows in early lactation. Like glucose metabolism, adjustments in lipid metabolism result from changes in the way adipose tissue responds to acute signals, such as to insulin and other hormones (3, 16, 40).

In addition to the direct metabolic effects that somatotropin coordinates, it stimulates the release of other compounds with metabolic effects, most notably insulin-like growth factor I (IGF-I). IGF-I probably mediates the effects of somatotropin on animals such that the cellular rate of milk synthesis is increased and the rate at which mammary cells die is decreased, thus causing higher daily milk yields for a longer period of time during the

2 Evidence in lactating dairy cows suggests that glucose use by tissues other than the mammary gland is decreased when somatatropin is administered. It is still not clear whether glucose use by skeletal muscle is decreased in growing pigs (3, 16).

Table 3-l—Effect of bST on Specific Tissues and Physiological Processes in Lactating Cows[a]

Tissue		Process affected during first few days and weeks of supplement
Mammary	↑	secretory activity and maintenance of mammary glands
	↑	blood flow and nutrient uptake
	↑	synthesis of milk with normal composition
Liver	↑	production of glucose
	o	response to acute signals (e.g., insulin) that allow for greater glucose production
Adipose	↑	mobilization of fat stores to meet needs for increased milk production if nutrient intake is inadequate
	↓	use of nutrients for fat storage so that they can be used for increased milk production if nutrient intake is adequate
	o	response to acute signals (e.g., insulin and other hormones that affect lipid metabolism) that allows for synthesis and breakdown of body fat reserves to be coordinated with changes in use and availability of nutrients
Muscle	↓	uptake of glucose
Pancreas	0	insulin and glucagon secretion reponse to changing glucose levels
Kidney[b]	↑	production of 1,25 vitamin D_3
Intestine[b]	↑	absorption of Ca, P and other minerals required for milk
	↑	ability of 1,25 vitamin D_3 to stimulate calcium binding protein
	↑	calcium binding protein
Whole body	↓	use of glucose by some organs so more can be used for milk synthesis
	↑	use of fat stores for energy if nutrient supply is Inadequate
	↓	use of nutrients to make body fat if nutrient supply is adequate
	ø	insulin and glucagon clearance rates
	ø	energy expenditure for maintenance
	↑	energy expenditure consistent with Increase In milk yield (i.e., heat per unit of milk not changed)
	↑	cardiac output consistent with increases in milk yield
	↑	productive effidency (milk per unit of energy intake)

[a]Changes (↑=increased, ↓=decreased, ø=no change, o=change) that occur in initial period of bST supplement when metabolic adjustments occur to match the increased use of nutrients for milk. With longer term treatment voluntary intake Inceases to match nutrient requirements. demonstrated in nonlactating animals and consistent with observed performance in lactating cows.

SOURCE: D.E. Bauman, 'Bovine Somatotropin: Review of an Emerging Animal Technology," commissioned background paper for the Office of Technology Assessment, Washington, DC, 1991.

lactation cycle ***(3).*** In growing animals, IGF-I stimulates cell proliferation in a variety of tissues (bone, muscle, connective, and adipose tissue) and increases protein synthesis in muscle (16, 40).

Poultry Somatotropin

Research using somatotropin to enhance growth and carcass composition in poultry (i. e., chickens, turkeys, and ducks raised for meat and egg production) is limited. Earliest research involved chickens that had their pituitary glands removed. Administration of chicken somatotropin (cST) was shown partially to restore growth. Chicken somatotropin also has been shown to increase circulating levels of IGF-I (40).

Administration of cST to broiler chickens[3] (i .e., chickens marketed at 6 to 7 weeks) has not been shown to influence growth, feed efficiency, or carcass composition. In young (post-hatched) chicks, the binding of somatotropin to its receptors in the liver is very low, whereas in adult chickens high somatotropin binding has been observed. There appear to be low somatotropin receptor numbers and/or receptor affinity for somatotropin during the early stages of chicken growth, potentially up to the time when broiler chickens are marketed. This might provide an explanation as to why cST has little or no effect in young broiler chickens. The basis for this low binding is not known, but some evidence exists that somatotropin itself regulates the number of somatotropin receptors (40).

While most studies have reported no enhanced growth in young chickens given cST, one study using daily injections of intermediate doses of native cST did elicit improved growth in 4-week-old broiler chickens. This raises the possibility that diet, frequency of cST administration, molecular form of cST, or dose may be necessary conditions to achieve a growth response in broiler chickens. Thus, it cannot be ruled out that optimal conditions have not been employed in most studies. Based on the evidence to date, however, cST administration appears not to be an effective means of promoting growth or productive efficiency in growing broiler chickens (40).

Administration of cST to roaster chickens (i.e., chickens more than 8 weeks old) has been shown to stimulate growth and feed efficiency while reducing carcass fat. The effects of cST on breast meat weight varied depending on the method of cST administration. For example, the weight of the breast meat was reduced when cST was administered in a pulsatile (rhythmic dripping) fashion, but increased when administration was by continuous infusion or daily injection. The extent of growth and of fat tissue accumulation also varied with method of administration and age of the chicken. These results suggest that cST can be used to improve roaster-age

[3]Chicken somatotropin derived from chicken pituitary glands and from recombinant DNA procedures were tried

chickens, but that the mode of administration and dose, and potentially diet, need to be optimized to achieve consistent results (40).

Turkeys that have had their pituitary glands removed have been treated with bST and cST; neither influenced growth. Administration of chicken or turkey somatotropin to intact turkeys has not been adequately explored.

Some evidence exists that bST or pST injections into the egg increase the growth and feed efficiency of male chickens after hatching, and reduce abdominal fat in both male and female chickens.

In summary, it has not been definitively demonstrated that somatotropin can be used to improve growth, feed efficiency, or carcass composition of poultry. More research is needed to determine if this is in fact the case, to optimize conditions needed to achieve growth, and to improve the mode of administration. There is a general lack of research on poultry biology and much basic research is needed to understand growth mechanisms in poultry. There is also a need to characterize fully the structure and control of the receptor(s) for chicken somatotropin, to identify the specific amino acid sequence of somatotropin that binds to the receptors, to understand the signal system used for somatotropin to elicit its biological response, and to identify hormones that may counteract the effects of somatotropin in poultry. Given the state of the art, it is unlikely that cST will be available for poultry production before the later part of the 1990s (40).

Porcine Somatotropin

Pigs administered porcine somatotropin (pST) for a period of 30 to 77 days have been shown to increase average daily weight gains by approximately 10 to 20 percent; improve feed efficiency by 15 to 35 percent; decrease adipose (fat) tissue mass and lipid formation rates by as much as 50 to 80 percent; and concurrently increase protein deposition by as much as 50 percent, without adversely affecting qualities such as taste and texture of meat. Prolonged release formulations and daily injections produced similar growth rates and feed efficiencies. In addition, similar growth rate increases were observed in both barrows (castrated male pigs) and growing gilts (immature female pigs) (16).

Daily administration of pST to gilts weighing between 110 and 220 pounds did not affect the age at which puberty occurred, the proportion of gilts reaching puberty prior to 240 days, or the pregnancy rate. One study did indicate that with pST administration, ovarian function was impaired in prepubertal gilts, and that the onset of puberty was delayed. Withdrawal of pST restored normal reproductive function (16).

The minimally effective dose of pST needed to increase growth performance is approximately 20 micrograms of pST per kilogram of body weight per day. In the commercial setting, pigs will likely be treated with pST for about 60 days during the growing-finishing period (16).

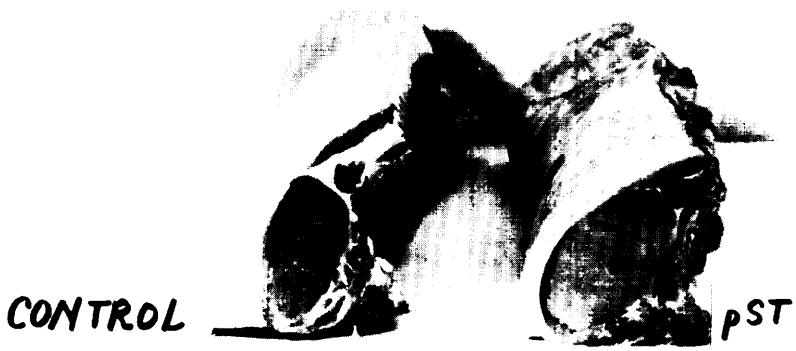


Photo credit: Terry Etherton, Pennsylvania State University.

Comparison of pork loins that show the effect of pigs treated with porcine somatotropin (PST). The loin-eye area of the loin treated with PST is 8 square inches; the control is 4.5 square inches.

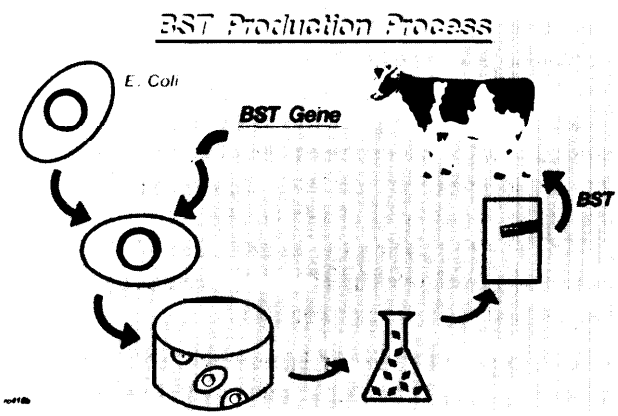
For effective use of pST, prolonged release formulations lasting at least 30 days need to be developed. Optimal nutrient requirements need to be determined. Initial data indicate that the diet should contain about 1.2 percent lysine ***(6).*** Current corn-soybean meal formulations containing about 16 percent crude protein may need to be supplemented with additional lysine, and perhaps other amino acids. Total feed intake will likely increase by 10 to 15 percent with pST administration. The nutritional requirements of pST-treated pigs is currently being studied by the National Research Council.

One **study** found that porcine somatotropin increased milk production between days 12 and 29 of lactation and the nursing piglets have a greater weight gain which matched the increased milk yield (16). However, this increase in milk yield and piglet weight gain has not been consistently observed (2, 8, 9, 10, 11, 42, 43, 44). Also, in some cases, adverse health effects were noted in pST treated sows (10, 42). Porcine somatotropin is currently being reviewed by FDA for commercial use. (For additional information on pST and its effects on carcass grades, see ch. 14.)

Bovine Somatotropin

Bovine somatotropin (bST) is currently undergoing FDA review for use in lactating dairy cows to increase milk production (figure 3-1). While individual milk yields depend on the management ability of the producer, on average, gains of about 12 percent can be expected with bST administration. However, response varies with the stage of lactation. Administration of bST early in lactation (i.e., immediately following parturition and prior to peak milk yield) evokes a small or negligible response (3). Administration after peak milk yields evokes a high response due to an immediate increase in milk yield, and a reduction in the normal decline in yields that occurs as lactation progresses. Maximum milk response is achieved with a daily bST dose of about 30 to 40 mg/day. BST does not alter the gross composition of the milk. The fat, glucose, protein, mineral, and vitamin composition of the milk all fall within the range of values normally observed in milk from cows not given bST (3).

Figure 3-l—Bovine Somatotropin (bST) Production Process



SOURCE: Elanco, a division of Eli Lily

The relative ratio of nutrient requirements of cows administered bST do not change, but the cow will eat more feed to accommodate the increased milk production. The magnitude of the increase in feed intake depends on how much milk production increases and on the energy density of the diet.

BST decreases pregnancy rates (proportion of cows becoming pregnant) and increases days open (days from parturition to conception). Conception rates (services per conception) are not altered. The effects observed are similar to those occurring in high milk producing cows that do not receive bST (3). The implications of using, bST in dairy production are discussed more thoroughly in OTA's 1991 publication U.S. *Dairy industry at a Crossroad: Biotechnology and Public Choices (47).*

A small number of studies using somatotropin to increase growth in growing cattle has been conducted, but research in this area is increasing. Results to date are highly variable due to the fact that studies differ significantly with respect to source and type of somatotropin used; dose and potency of somatotropin; route and frequency of administration; number, sex, type, and age of animals; duration of treatment; level and type of nutrition; and methodology used to determine characteristics measured. Thus, comparisons are tenuous, but on average, administration of somatotropin to growing cattle increases average daily weight gain by" 12 percent, improves feed conversion efficiency by 9 percent, increases carcass lean content by 5 percent, and decreases carcass fat content by 15 percent (15). Additional long-term studies are needed. Optimal dose, nutritional needs, duration, and withdrawal period before slaughter need to be determined.

Ovine Somatotropin

A small number of studies has examined ovine somatotropin (oST) or bST for use as a growth promotant in sheep. Because oST and bST are similar on amino acid sequence they both are effective. Like the studies with growing cattle, investigations with sheep vary sig-

nificantly in design and methodology. These studies suggest that on average, administration of somatotropin to sheep will increase the average daily weight gain by 18 percent, improve the feed conversion efficiency by 14 percent, increase the carcass lean content by 10 percent, and decrease carcass fat content by 15 percent.

Ruminants present some special challenges with regard to supply of amino acids to support high rates of protein accretion. Recent studies with growing cattle and lambs demonstrate that nutritional constraints imposed by rumen fermentation may limit amino acid supply and ultimately the biological response to somatotropin (4, 2 1). Long-term studies are needed, and optimal conditions of somatotropin administration and nutrient requirements must be determined (15).

Fish Somatotropin

Recombinant trout somatotropin injected into yearling rainbow trout increased growth rates by 100 percent as compared to control fish. Body length increased, and the chemical composition of the muscle tissues was indistinguishable from that of the controls (34). However, injection into individual fish is inefficient and different modes of administration are needed. Other studies have tried dipping and incubating test fish in an appropriately balanced salt solution containing fish somatotropin. Results have been encouraging; within 5 weeks, body weight had increased by 1.6 times over that of controls (34).

Evidence exists that invertebrates also produce somatotropins. Somatotropin from abalone has been isolated and shown to enhance growth in juvenile abalone. Recombinant trout somatotropin has been shown to increase the size of oysters (34).

Somatotropin also can be used to increase growth in finfish and shellfish. Research is needed to determine the most effective and practical means of administration. Large-scale production and purification of recombinant fish somatotropin is paramount. Optimum dose, nutrient requirements, and other related conditions must be established for each target species. Most studies to date have been short-term studies. Long-term studies to understand the effects of somatotropin on fish must be conducted. Given the work that is still needed, it is unlikely that somatotropin will be used commercially in the fish industry before the second half of the 1990s.

Somatotropin Related Technologies

Recognition of the role that somatotropin plays in growth and milk production has led researchers to search for means to increase endogenous levels of somatotropin in livestock as an alternative to administration of exogenous somatotropin.

The production and secretion of somatotropin by the pituitary gland is controlled by another protein hormone called growth hormone releasing factor (GRF). Early studies in pigs involved daily injections of 30 micrograms of GRF. Neither growth rate nor feed efficiency was significantly improved. There was a significant improvement in carcass composition (less fat), although the improvement was not as great as with exogenous administration of porcine somatotropin. Using synthetic analogs of GRF that are resistant to degradation by protease enzymes elicits a greater reaction; daily weight gain and feed efficiency increased, and carcass composition changed in a manner similar to that which occurs with exogenous administration of porcine somatotropin (16). There is some evidence that GRF does elicit some effects that are different than those of somatotropin. For example, a small improvement in the digestibility of dietary dry matter has been observed in GRF-treated cattle and this has not been routinely observed with bST-treatment (3, 16). GRF itself can be produced in bacteria, but some of the synthetic analogs cannot, and alternative methods will be required to produce sufficient quantities for commercial use. It is not expected that GRF will be commercially available before the later half of the 1990s.

An alternative way to increase endogenous somatotropin levels is to block compounds that prevent the secretion of somatotropin. Release of somatotropin from the pituitary gland is blocked by a compound called somatostatin. Deactivating somatostatin will increase the levels of somatotropin in the animal. Somatostatin is deactivated by stimulating the animal to produce antibodies to this compound. The process involves coupling somatostatin with another compound that stimulates the immune system in animals. Administration of this coupled compound to an animal causes the animal to produce antibodies that bind to somatostatin and deactivate it, thereby preventing it from inhibiting the release of somatotropin from the pituitary. When used in pigs, this process doubled the concentration of porcine somatotropin and increased growth rates slightly, but it is likely that higher somatotropin levels will be needed to increase growth in pigs significantly. In cattle, use of this method increased growth rates by 10 to 17 percent and improved feed efficiency by 13 percent (16).

A third possible way of increasing the effectiveness of somatotropin is to couple somatotropin with a monoclinal antibody specific for somatotropin. In dwarf mice

that have deficient pituitary glands, a somatotropin-monoclonal antibody complex increased weight gains 400 to 600 percent more than administration of somatotropin alone (16). In lactating sheep, a somatotropin-monoclonal antibody complex increased milk production more than somatotropin alone (16). The mode of action is not known with certainty. It is speculated that the complex is selectively recognized by different target tissues and receptors in preference to somatotropin alone. It is possible that the monoclinal antibody inhibits the receptor from internalizing the somatotropin, which allows the somatotropin to be active for a longer period of time. The use of monoclinal antibodies from species other than the animal being treated, however, may cause an immune response by the animal.

Beta-Agonists

Beta-agonists (also called beta-adrenergic agonists) are compounds similar to adrenaline. They are generally of two types, the beta- 1 agonists that stimulate cardiovascular functions and the beta-2 agonists that regulate smooth muscle function. Beta-agonists are currently used in humans to control bronchial asthma and to relax premature uterine contractions.

Beta-agonists can also act as repartitioning agents. They redirect nutrients away from the formation of adipose tissue (fat deposits) and towards muscle growth (48). Almost all cells have beta-adrenergic receptors. interaction of beta-agonists with the cell membrane receptors initiates intercellular responses that affect fat and protein metabolism and accretion.

Beta-agonists are not currently approved for use as livestock growth promotants in the United States. At least three companies have tested beta-agonists to promote growth and enhance carcass leanness in meat-producing animals. Beta-agonists tested include clenbuterol and cimaterol in lambs, beef, swine, and broilers (American Cyanamid); salbutamol in swine (Glaxo Animal Health, United Kingdom) and ractopamine hydrochloride in finishing swine, beef and turkeys (Eli Lily and Co.). Results of early studies with clenbuterol, cimaterol, and salbutamol were variable and available evidence suggests that none of these compounds are under development as growth promotants for livestock application (48).

Eli Lilly and Company is developing ractopamine hydrochloride to enhance carcass leanness and promote growth in meat-producing animals. In finishing swine (i.e., pigs weighing 100 to 250 pounds), ractopamine is administered as a feed additive, at doses of 5 to 20 parts per million (ppm), usually for a period of 42 to 49 days. Ractopamine is registered under the trade name Paylean, and is currently undergoing FDA review (48).

Trials involving finishing pigs were conducted in the United States, Canada, and several other countries worldwide. Ractopamine increases the rate of daily weight gain (maximum of 8.9 percent), decreases feed consumption (average of 3.9 percent), and improves feed conversion (up to 12.3 percent over untreated controls). [5] Additionally, two measures of carcass leanness—loin eye leanness and the 10th rib fat thickness—improved by a 14.9 percent increase and 13.6 percent decrease, respectively. Total lean content of the carcass increased from 50.9 percent to 56.9 percent as determined by total carcass dissection. Swine with superior genetics for leanness show a greater response to ractopamine than those with low lean-gain potential. Visual and taste panel evaluations of meat palatability characteristics from the ractopamine-treated pigs appear to be unchanged (48).

While total feed consumption decreases slightly, use of ractopamine requires crude protein levels greater than current National Research Council recommendations for finishing swine. Rations containing 16 to 20 percent crude protein or lysine equivalent appear to optimize the growth performance response to ractopamine. However, carcass leanness effects are seen at lower crude protein levels. Addition of fat to the diet, a common practice in swine, did not affect carcass leanness, daily weight gain, or feed conversion responses to ractopamine (48).

Some reports have indicated that beta-agonists cause hoof lesions in swine. No such effects were observed in another study with ractopamine given in amounts up to 25 times the highest intended level of use (550 ppm). Similarly, at three times the intended use level (60 ppm) during the finishing phase, there were no observed effects on the subsequent percent of gilts in heat, the percent

[4] Clenbuterol is currently marketed in Europe, Mexico, Canada, South America, and Asia as a veterinary prescription drug to treat bronchial and smooth muscle disorders in animals (primarily race horses and sheep). It has not been approved for use in the United States. Salbutamol is marketed as an anti-asthmatic in humans (17, 48).

[5] Twelve trials involving 1278 barrows and gilts were fed rations of 16 percent crude protein and administered ractopamine as a feed additive in quantities up to 20 parts per million.

farrowing rate, the number of live or dead newborn pigs, the 21-day pig weaning weight, or gilt weights at the end of the nursing period (48).

Antimicrobial Agents

Biotechnology is being used to produce new compounds that can enhance livestock production, but traditional means will continue to be used for the same purpose. One such traditional method is the addition of antimicrobial agents to livestock feed. Antimicrobial agents are compounds that, when administered in low concentrations, suppress or inhibit the growth of microorganisms. Antimicrobial agents include antibiotics (naturally occurring substances produced by yeasts, molds, and other microorganisms) and chemotherapeutic (substances that are chemically synthesized). Copper also has antibacterial properties when present in relatively high concentrations.

Antimicrobial have been widely used as feed additives for swine, poultry, beef cattle, and dairy calves since the early 1950s and numerous trials have been conducted during that time to document the efficacy of antibiotic use. Approximately half of the 4.65 million kilograms of antibiotics and chemotherapeutic sold in the United States in 1988 were for nonmedicinal use (12). In the early 1980s, it was estimated that approximately 75 percent of pig feeds, 80 percent of poultry feeds, 60 percent of feedlot cattle feeds, and 75 percent of dairy calf feeds contained antimicrobial agents (12). An estimated 90 percent of all feedlot cattle are administered antibiotics (12). Today, approximately 88 percent of the antibiotics used in livestock are given at subtherapeutic levels to promote growth, improve feed utilization, reduce mortality, reduce liver abscesses, and improve reproductive efficiency. Currently, 14 antibiotics and 6 chemotherapeutic have been cleared by the FDA for use as livestock feed additives (table 3-2).

The exact mechanism by which antimicrobial stimulate growth is not known with certainty. Three mechanisms have been proposed: a metabolic effect, a nutritional effect, and a disease control effect. Various antimicrobial have been shown to affect water and nitrogen excretion, to inhibit oxidation reactions that require magnesium ions, and to increase protein synthesis in muscle cells. However, none of these metabolic effects is significant enough to account for the observed increases in growth (12).

The nutritional effect is based on the premise that certain intestinal microbes synthesize vitamins and amino acids essential to animals, while others compete with the host animal for these nutrients. Shifts in the intestinal population of bacteria associated with the use of antibiotics could result in greater availability of nutrients for the host animal. Some antibiotics have been shown to stimulate yeast growth and bacteria that produce vitamins while reducing population levels of lactobacilli, bacteria that require amino acids in the same proportions as pigs and chicks.

Increased intestinal wall thickness and total gut mass, thought to be caused by bacterial invasion or toxins, are reduced by antibiotics. This decreased mass possibly leads to greater nutrient absorption and increases diversion of energy and nutrients away from heat production by the gut to body growth.

Evidence exists to support the hypothesis that the dietary protein requirements of animals administered antibiotics are lower than those of control animals. The most striking evidence in support of the nutritional effect is seen with the ionophore class of antibiotics, which causes an increase in propionic acid and a decrease in acetic acid in the rumen. Biosynthetic pathways using propionic acid are energetically more efficient than those using acetic acid, which could account for the marked reduction in feed requirements per unit of gain for animals administered the ionophores.

The most widely accepted theory as to how antimicrobials promote growth is the disease-control effect.

Table 3-2—Antimicrobial Agents Approved as Growth Promotants for Swine, Poultry, and Cattle in the United States[a]

Antibiotics	Chemotherapeutics
Bacitracin zinc (S,P,C)	Arsanilic acid (S,P)
Bacitracin methylene disalicylate (S,P)[b]	Carbadox (S)
Roxarsone (S,P)	Sodium arsanilate (S,P)
Bambermycins (S,P)	Sulfamethazine (S,C)
Chlortetracycline (S,P,C)	Sulfathiazole (S)
Erythomycin (P)	Lincomycin (S,P)
Lasalocid (C)[c]	
Monensin (C)[c]	
Oxytetracyline (S,P,C)	
Penicillin (S,P)	
Streptomycin (S,P)	
Tiamulin (S)	
Tylosin (S)[b]	
Virginiamycin (S,P)	

[a]The letters in parenthesis refer to the species for which the drug is approved; S = swine, P = poultry, and C =cattle.
[b]Bacitracin methylene disalicylate and tylosin are also approved in cattle to reduce liver abscesses.
[c]Lasalocid and Monensin are approved for use in poultry to control coccidiosis.

SOURCE: Office of Technology Assessment, 1992.

Antibiotics control subclinical disease, thereby allowing animals to more closely approach their genetic growth potential. The fact that antibiotics stimulate growth more in young animals than older animals provides some support for this theory because young animals have lower immunological competency and are more susceptible to disease. Also, the degree of the growth response is strongly influenced by the cleanliness of the living environment and the disease load of the animals involved.

Most of the research concerning antimicrobial is conducted at the pharmaceutical firms that develop these products. Research at universities evaluates the efficacy of already approved antimicrobial agents under different housing, management, and feeding programs. Some clinical studies of compounds in development are also conducted at universities.

Current research is focusing on the development of new antimicrobial, new techniques for screening and evaluating the safety of antimicrobial, detection of residues in meat, and the possible spread of antimicrobial resistance. Genetic engineering techniques can be used to alter the production of antibiotics by bacteria and to develop nucleic acid probes for use in safety evaluation.

Other research is focusing on ways to improve the efficiency of nutrient utilization and microbial fermentation in the gastrointestinal (GI) tract. Techniques that modify membrane function in bacteria can increase the transport of ions and substrates into bacterial cells, which could enhance digestion in ruminants. Alternatively, the use of live antagonistic microorganisms in feed can be used to maintain the optimal microflora.

More efficient methods of delivering antimicrobial, including intraruminal delivery devices, boluses, and rotation of two or more agents, are being developed. The compatibility and synergism of antimicrobial combinations and the effect of the diet are also being explored (12).

Antimicrobial Use in Poultry

Antimicrobial use in chickens up to 4 weeks old increases growth rate and feed efficiency by approximately 7 and 4 percent, respectively. Older chickens also show improvement, although not as high. Young turkeys have shown improved growth rates and feed efficiency of approximately 13 and 7 percent, respectively. When antimicrobial are used in laying hens, egg production improved by up to 4 percent, the feed required per dozen eggs was reduced up to 5 percent, and matchability improved about 3 percent. Similar results were obtained in turkeys. Antimicrobial use also appears to reduce mortality (12).

Antimicrobial Use in Swine

In pigs, antimicrobial have been shown to increase growth rates, reduce feed requirements per unit of weight gain, and reduce mortality and morbidity. Smaller (younger) pigs respond more to antibiotics than heavier pigs. Antibiotics have been found to improve growth rate of pigs weighing between 7 and 25 kg by 16 percent and to reduce the amount of feed required per unit of gain by 7 percent. In slightly heavier pigs (from 7 to 49 kg), the improvements in weight gain and feed efficiency were 11 and 5 percent, respectively. Over the entire growing-finishing period, antibiotics improved weight gain by 4 percent and feed efficiency by 2 percent. Improvements in growth rates, feed efficiency, and mortality rates from antibiotic use are greater under farm conditions than in highly controlled test conditions at universities and research stations. In addition, the effectiveness of antibiotics has not diminished over 40 years of use (12).

Copper gives growth rate and feed-efficiency utilization rates similar to those of antimicrobial, and in young pigs a combination of copper and antimicrobial appears to have an additive effect.

Antimicrobial are not usually continuously administered to breeding animals, but during certain critical stages of the reproductive cycle, such as at the time of breeding, administration of antimicrobial can improve conception rates (by about 7 percent) and increase litter size (by about a half a pig). Use of antimicrobial at farrowing reduces the incidence of uterine infections. Data also indicate a slight improvement in the survival and weight gain of nursing pigs that have been given antimicrobial in prefarrowing and lactation diets. Evidence also exists that the withdrawal of antibiotics from animals that have been administered antibiotics for a long time is associated with a reduction in reproductive performance (12).

In the last 5 years, two new antibiotics were cleared for use in swine. Three more antibiotics are currently under development (12).

Antimicrobial Use in cattle

In beef, growth rates have increased up to 5 percent, and feed efficiency gain has increased up to 7 percent with antimicrobial use. Antimicrobial are also commonly used to reduce, by nearly half, the incidence of liver abscesses. Animals with abscessed livers gained

weight more slowly than those without abscessed livers—about 1/3 pound per day less. Antimicrobial can be used to improve weight gain in dairy calves. but no general beneficial response has been noted in lactating cows (12).

Anabolic Steroids

Steroids are a class of lipid compounds composed of four interconnected rings of carbon atoms linked with various functional groups. Some steroids act as vitamins while others act as hormones. The anabolic steroids used to promote growth are estrogens and progesterone (female sex hormones) and androgens (male sex hormones). Steroids have been demonstrated to promote growth, increase feed efficiency, increase lean meat production, and reduce carcass fat. These hormones have been demonstrated to have growth-promoting properties in beef, sheep, swine, poultry, and fish. Such effects are greatest in ruminants.

Anabolic steroids were first approved for use in livestock in 1954. Currently they are approved for use as growth promotants in the United States only for beef and sheep. It is estimated that 10 percent of heifers and 60 percent of steers are treated with anabolic steroids as calves; 70 percent of stocker cattle; and 90 percent of feedlot cattle are administered anabolic steroids (35). Anabolic steroids reduce the cost of producing beef by an estimated $17 per head, and a complete ban on anabolic steroids in the United States would result in an estimated net-return loss of $2.4 to $4.1 billion in beef and sheep products (35).

Anabolic steroids are used in the United States either singly or in combination, with the most common method of administration being a prolonged release implant inserted at the base of the ear (see table 3-3). A combination estradiol-trenbolone acetate implant is currently under FDA review.

The mechanisms by which steroids act in livestock are still not known with certainty, despite the fact that these compounds have been used for nearly 40 years. It has generally been postulated that estrogens stimulate the production and release of somatotropin from the pituitary gland, and that the increased sornatotropin, in concert with insulin, increases the uptake of amino acids and the synthesis of muscle protein (35).

New studies indicate, however, that estrogens and somatotropins are additive, and act independently, and therefore it is unlikely that the action of estrogens occurs via elevated levels of endogenous somatotropin. This evidence has led to the proposal of alternative hypotheses. One such proposal postulates that because there are estrogen receptors in bovine skeletal muscle, estrogens could directly bind to these receptors and stimulate protein synthesis (35).

Alternatively, estrogens may stimulate the somatotropin receptor sites in the liver; greater binding and receptor capacity has been observed following estradiol administration. However, estrogens do not elicit an anabolic response in rats despite the fact that they stimulate somatotropin release and there are estrogen receptors present in rat skeletal muscles. This evidence suggests that the mode of action of estrogens may in fact be different than any of those hypothesized (35).

Table 3-3—Anabolic Steroids Commercially Available in the United States

Anabolic steroid	Commercial name	Method of use
Estrogens		
Beta-estradiol	Compudose	Implant
Zeranol[a]	Ralgro	Implant
Androgens		
Trenbolone acetate		Implant
Progesterone		
Melengesterol acetate		Feed additive
Combination		
Beta-estradiol/testosterone	Synovex-H	Implant
	Heifer-oid	Implant
Beta-estradiol/progesterone	Synovex-S	Implant
	Synovex-C	Implant
	Steer-oid	Implant

[a]Zeranol is technically not an estrogen (it's produced by a fungus) but has estrogenic properties.

SOURCE: Office of Technology Assessment, 1992

Most androgens have not consistently shown anabolic activity in ruminants, although trenbolone acetate (TBA) used alone, and especially when combined with estrogens. gives good response. TBA significantly elevates plasma estradiol levels, which may explain at least part of its activity. Androgens are thought to work by blocking muscle receptors for another class of hormones, the corticoid hormones. This decreases muscle protein degradation and turnover, rather than increasing protein synthesis (35).

The pharmaceutical industry conducts most anabolic steroid research. Universities conduct some research concerning the mechanism of action of steroids and work in conjunction with the pharmaceutical industry to conduct clinical trials. Current research is focusing on using combinations of steroids and on methods to improve timed-release implants so that they release lower levels immediately following implantation and continue to release for a longer period thereafter. Researchers are also exploring the possibility of administering androgens to pregnant ewes and cows in the hope of increasing growth potential in the offspring (a process known as imprinting). Imprinting has been shown to improve growth. feed efficiency, and carcass leanness in female offspring, but leads to no observed changes in castrated male offspring (35).

A clearer understanding of the mechanism of action of anabolic steroids is needed. Research is also needed to determine the optimum dose of steroids required to maximize anabolic response. Current dosage rates are *14* to 36 mg for estrogens, 200 mg for progesterone, 200 mg for testosterone, and 140 to 200 mg for trenbolone acetate, administered by implants lasting for 90 to 120 days. These doses are probably lower than those that would yield maximum growth; however, to change dosage would require FDA approval (35). Determining optimal dosage for maximum anabolic effects might also help determine the mode of action of these steroids and whether steroids are additive in effect with other hormones.

Further research is needed to determine the nutrient requirements for maximum response and to determine the effects of steroids on meat marbling. Anabolic steroids do not appear to affect the texture, flavor, juiciness. or cooking loss of meat, but some controversy remains concerning the effect of steroids on carcass quality, marbling, and carcass grade, particularly with respect to TBA/estradiol combination (35).

REPRODUCTION TECHNOLOGIES

The field of animal reproduction is undergoing a scientific revolution. For example, it is currently possible to induce genetically superior cows to shed large numbers of eggs (superovulation). It is also possible to fertilize these eggs in vitro with the sperm of genetically superior bulls. Each resulting embryo can then be sexed and split to produce multiple copies of the original embryo, frozen for later use, or transferred to recipient ''surrogate' cows whose reproductive cycle has been synchronized to accept the developing embryo. In the near future, it may be possible to sex the sperm rather than the embryo and to create greater numbers of copies of each embryo than is currently possible. Embryos produced by new reproductive methods are currently being marketed. Techniques now being developed will make it easier to insert new genes into the embryos to produce transgenic[6] animals. Although as yet no transgenic farm animals are commercially available, these new technologies are being used to improve the quality of livestock herds more rapidly than could be achieved with traditional breeding. Currently, however, many of these technologies are still relatively inefficient.

Estrous Cycle Regulation

Research has shed new light on the basic mechanisms controlling egg growth and maturation, and corpus luteum[7] function. This new knowledge is aiding the development of precise methods to regulate the estrous cycle, induce superovulation, and reduce the heavy losses due to early embryo deaths that occur in all domestic animals.

Perhaps the most important development in ovarian physiology in recent years is the discovery of the ovarian hormone inhibin, which decreases the ovulation rate. [8] Some breeds of animals with exceptionally high ovula-

'Animals whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm, using recombinant DNA techniques (46). Transgenic animals can be created that possess traits of economic importance including improved disease resistance, growth, lactation, or reproduction.

[7]The corpus luteum is a temporary endocrine organ that is produced at the site of ovulation during each estrous cycle. It produces hormones needed to maintain pregnancy.

[8]Inhibin decreases ovulation rates by suppressing the secretion of follicle stimulating hormone (FSH), a hormone produced by the pituitary gland.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Animal physiologist prepares an embryo for microscopic examination before implanting it into an animal.

tion rates, such as the Booroola strain of Merino sheep in Australia, are known to have low levels of circulating inhibin. Cattle immunized against inhibin have lower circulating levels in their blood and show increased ovulation rates, The genes controlling inhibin production have been cloned, and the potential exists for producing transgenic animals in which these genes are repressed or deleted (18).

Progress has also been made in understanding the control mechanisms that regulate corpus luteum function and its production of progesterone, a hormone that regulates the length of the estrous cycle and helps maintain pregnancy. Regulation of the estrous cycle is needed to ready surrogate mothers to receive embryos, and also to initiate superovulation. Estrous cycle regulation is reasonably well understood and developed in cattle and sheep. Conception rates in treated cows are similar to those obtained with animals bred at naturally occurring estrus. The estrous cycle of pigs appears to be more complex than that of ruminants and the process of controlling the cycle is not as efficient. Currently, superovulation treatments for cattle use highly purified hormones produced by recombinant DNA technology. About 10 viable eggs are produced, on average, per treatment (compared to the 1 egg a cow normally produces per ovulation) (18). As new knowledge of the factors controlling egg development and corpus luteum function is applied, the number of viable embryos produced by each superovulation treatment is expected to increase.

Once eggs are collected, they are matured and fertilized in vitro. In vitro fertilization occurs only when a capacitated sperm (i. e., a sperm specially prepared to penetrate the egg cell membrane) encounters an egg that is in an optimal maturation state. Great progress has been made in understanding the factors involved in egg maturation and sperm capacitating in livestock. As a result, in vitro fertilization rates as high as 70 to 80 percent are produced in cattle, swine, sheep, and goats, and offspring are successfully produced. Conception rates with superovulated and artificially inseminated eggs in cattle are the same as those obtained by artificial insemination of control animals bred at naturally occurring estrus. Embryos produced with these techniques are currently being marketed. It is estimated that about 100,000 calves are born annually in the United States as the result of embryo transfer techniques. Many more embryos are being exported (41).

Early detection of pregnancy can enhance a livestock producer's ability to identify and rebreed animals that have not become pregnant. Traditionally, pregnancy has been detected by rectal palpation. This procedure can be conducted at 40 days post breeding, but at this early date the possibility exists of damage to the fetus. In practice, rectal palpation is usually carried out at 60 days or later in cattle. An alternative method is to measure progesterone concentration in milk. Concentration can be measured at 20 days after breeding. However, the process is expensive and results in about 15-percent false positives. A new method under development involves using a radioimmunoassay procedure to detect protein B, a gly - coprotein produced by cells of the ruminant placenta (18).

High embryo mortality is a major cause of reproductive loss in all livestock. Embryos of all species must signal their mothers in some way to prevent regression of the corpus luteum, so that the progesterone secretion needed to maintain pregnancy can continue. Early pregnancy recognition signaling systems are complex and apparently differ from species to species. In ruminants, compounds similar to alpha interferon may be early signals of pregnancy. Administration of interferon early in pregnancy is being tested as a possible means of reducing

[9] Sperm capacitation involves the uptake of calcium ions which changes the pH of the sperm.

embryo loss. In mice and humans. platelet activating factor is known to be an early pregnancy reccognition signal. Preliminary data exist to suggest that it may play a role in early pregnancy in sheep and cattle (18).

Embryo Cloning

Multiple copies of a mammalian embryo were first produced by physically splitting an early embryo into halves. giving rise to identical twins (18). If the embryo) is dividemore than twice, however, few offsprings survive. Thus, no more than four indentical animals can be produced by splitting, and generally only two empryos are produced by this method. This procedure is already used in the cattle empryo transfer industry nearly doubling the number of offspring produced.

A more efficient and promising method of producing multiple copies of an embryo is a technique called nuclear transplantation. Basically, the procudure involves the transfer of a nucleus from a donor embryo into an immature egg whose own nucleus has been removed. The recipient egg cell is activated by exposuure to an electric pulse, allowed to develop into a multicelled embryo, and then used as a donor in subsequent nuclei.ir transplantations to generate multiple clones. This procedure (outlined in figure 3-2) has been used successfully with cattle, sheep, and swine. This technique has already produced hundreds of embryos that have been successfully carried to term in cattle. and recloning has resulted in as many as eight calves from one embryo (29).

The value of this technique is enhanced by the ability to transfer nuclei successfully from frozen embryos into eggs whose nuclei havc been removed. Conception rates obtained after transfer of embryos produced by neculear transplantation are varible, but rates us high as 50 percent have been obtained. However, embryo losses after transfer are higher than normal, resulting in actual pregnancy rates ranging from 15 to 33 percent (18). Combining the techniques of in vitro fertilization. embryo cloning, and artificial estrous cycle regulation can result in major changes in livestock breeding and in the rates of genetic improvement.

Embryo and Sperm Sexing

The availability of a technique to preselect the sex of the progeny holds great economic potential for the livestock industry. In the diary industry, females are the major income producers. while in the beef industry, males area economically more valuable. Until recently, no methods existed that provided the degree of separation needed for commercial use. However, recent advances in the seperation of the X and Y sperm, and sexing of the embryo have been made.

It has long been a goal of mammalian phsiologists to develop a method to effectively separte X and Y chromosome-bearing sperm to control the sex of the offspring. Most sperm seperation techniques are based on potential differenccs in the size and density of the two sperm types.[10] These methods, however have met with little success (41).

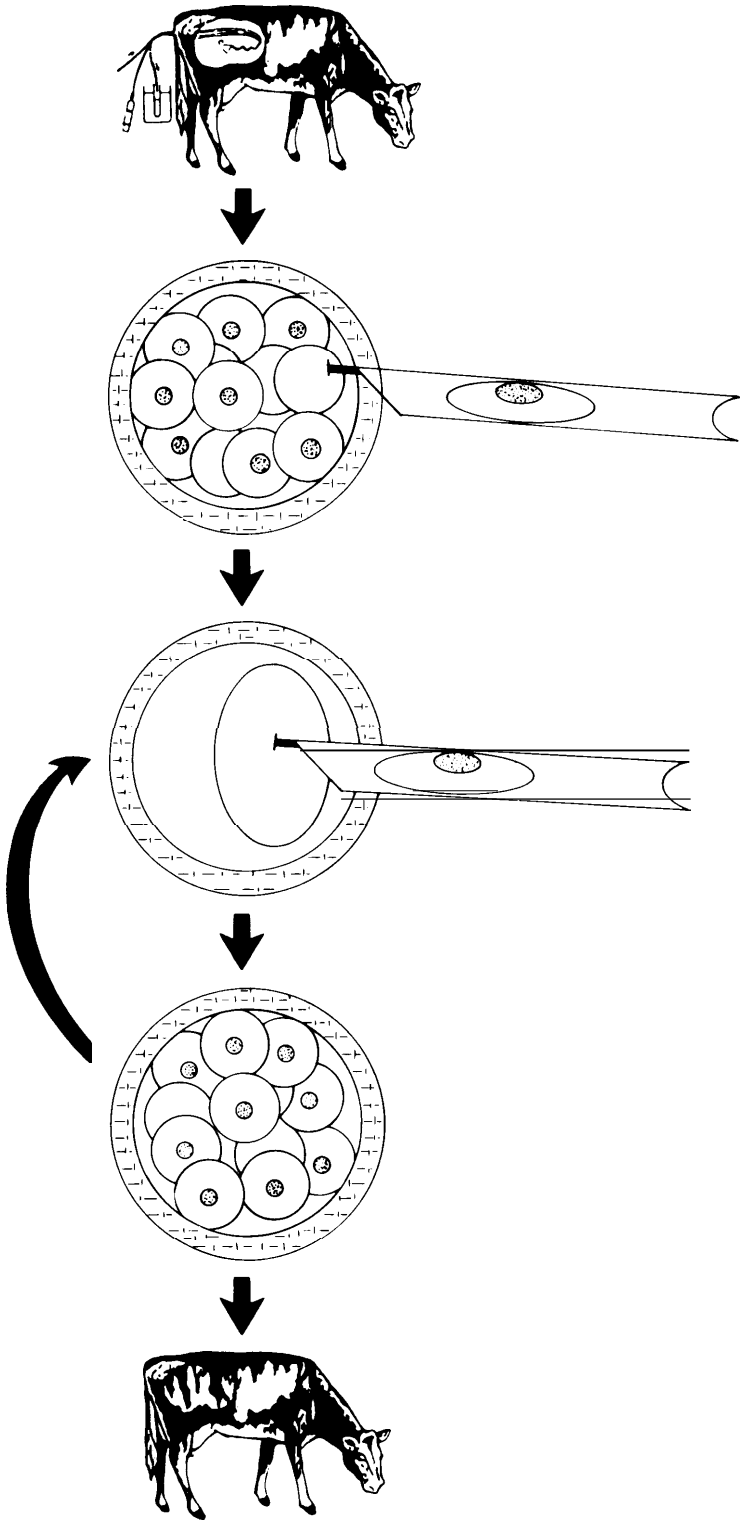
Development of cell-sorting techniques based on the differences in sperm size and Fluorescence of sperm DNA (flow cytometric measurements) has provied the first effective mehod to sort the sperm cellls. Johnsson et al. (22) recenently reported successful serperation of intact viable X and Y chromosome-bearing sperm using this method. Although the differece in DNA contents of the X and Y chromosome-bearing sperm in rabbits amounts to only about 3 percent. 94 percent of the rabbits (does) inseminated with X-bearing sorted sperm produced females and 81 percent of the does inseminated with Y-bearing sorted sperm produced males. This method has been used to separate X and Y bearing intact sperm of cattle. swine, and sheep with greater than 80-percent accuracy (2). Commercial use of this process is limited. at present. by the number of sperm that can be sorted per hour and by increased embryo mortality observed in the embryos produced after insemination with the sorted sperm. Neither of these factors is thought to represent an insurmountable difficulty.

The most accurate method of sexing embryos is to create a picture of the number, size, and shape of' the chromosomes contained in the embryonic cells, a process called karyotyping. However. this method requires removal of about half of the cells of early stage embryos, which decreases embryo viability and limits the number of embryos that can be transferred. Another method uses antibodies[11] to defect proteins (antigens) unique to male embryos. This method is not damaging to the embryos and encouraging results have been obtained in one laboratory; however, the technique yields variable results and has not been widely adopted (18).

[10] Methods used are differential sedimentation techniques including differential velocity sedimentation, free-tJow electrophoresis, and convection counter-stream ing galvanization.

[11] The antibodies are attached (labeled) to a flourescent compound to allow for detection.

Figure 3-2—Nuclear Transplantation



SOURCE: Office of Technology Assessment adapted from R S Prather and N L First. Cloning Embryos by Nuclear Transfer, Genetic Engomeeromg of *Animals,* W Hansel and B J Weir (eds.), *Journal of Reproduction and Fertility Ltd .* Cambridge, UK, 1990, pp 125-134

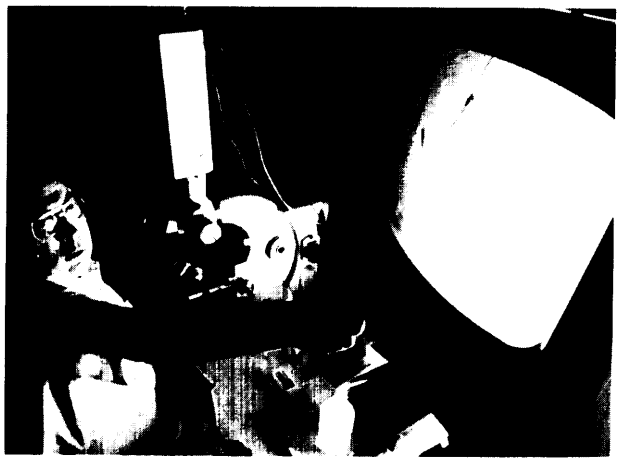


Photo credit: U.S. Department of Agriculture, Agricultural Research Service,

Animal physiologist checks swine sperm cells on video monitor to evaluate their motility, a procedure that precedes laser X-Y sperm separation.

More recently, the sex of bovine and porcine embryos has been determined by untempting to match fragments of DNA that are contained only on Y (male) chromosomes with the same DNA fragments in the embryo. Due to its chemical structure, a fragment of DNA will combine with a second DNA fragment that has a corresponding nucleic acid sequence. Therefore, a fragment of DNA that is specific to males can be used as a probe to identify male DNA fragments in the embryo. Combined with technologies that produce multiple copies of the DNA fragments, this method determines the sex of the embryo using only a few cells. It is rapid (about 6 hrs) and extremely accurate (up to 95 percent). but may be overtaken by the rapidly developing capability to separate X and Y chromosome-bearing sperm (18).

TRANSGENIC ANIMALS

The new reproductive technologies of superovulation, in vitro egg maturation and fertilization, nuclear transplantation. and embryo sexing can, and are being used to upgrade livestock herds. When these technologies are combined with recombinant DNA technologies (the identification, isolation, and transfer of selected genes), it becomes possible to produce animals containing foreign DNA **in** their germ lines (transgenic animals). (See figure 3-3.)

The tools of biotechnology provide the opportunity to develop transgenic livestock that contain genes coding for improved growth charticteristics, lactational performance, and resistance to disease and stress. Transgenic animals have human medical implications as well. It may be feasible to produce important pharmaceuticals in livestock. Only certain human drugs can be chemically synthesized or produced by bacteria, because some compounds undergo modifications after the protein has been produced (referred to as post-translational modifications). Animals are capable of performing these modifications. but bacteria are not. Transgenic animals can also serve as powerful research tools to understand genetic and physiological functions, and provide a model system with which to study human disease.

The production of transgenic animals is inextricably linked to the new reproductive technologics discussed in the previous section. lndeed, it is impossible to produce animals containing foreign DNA in their germlines without first manipulating the embryo and transferring it to a recipient animal.

Process of Creating Transgenic Animals

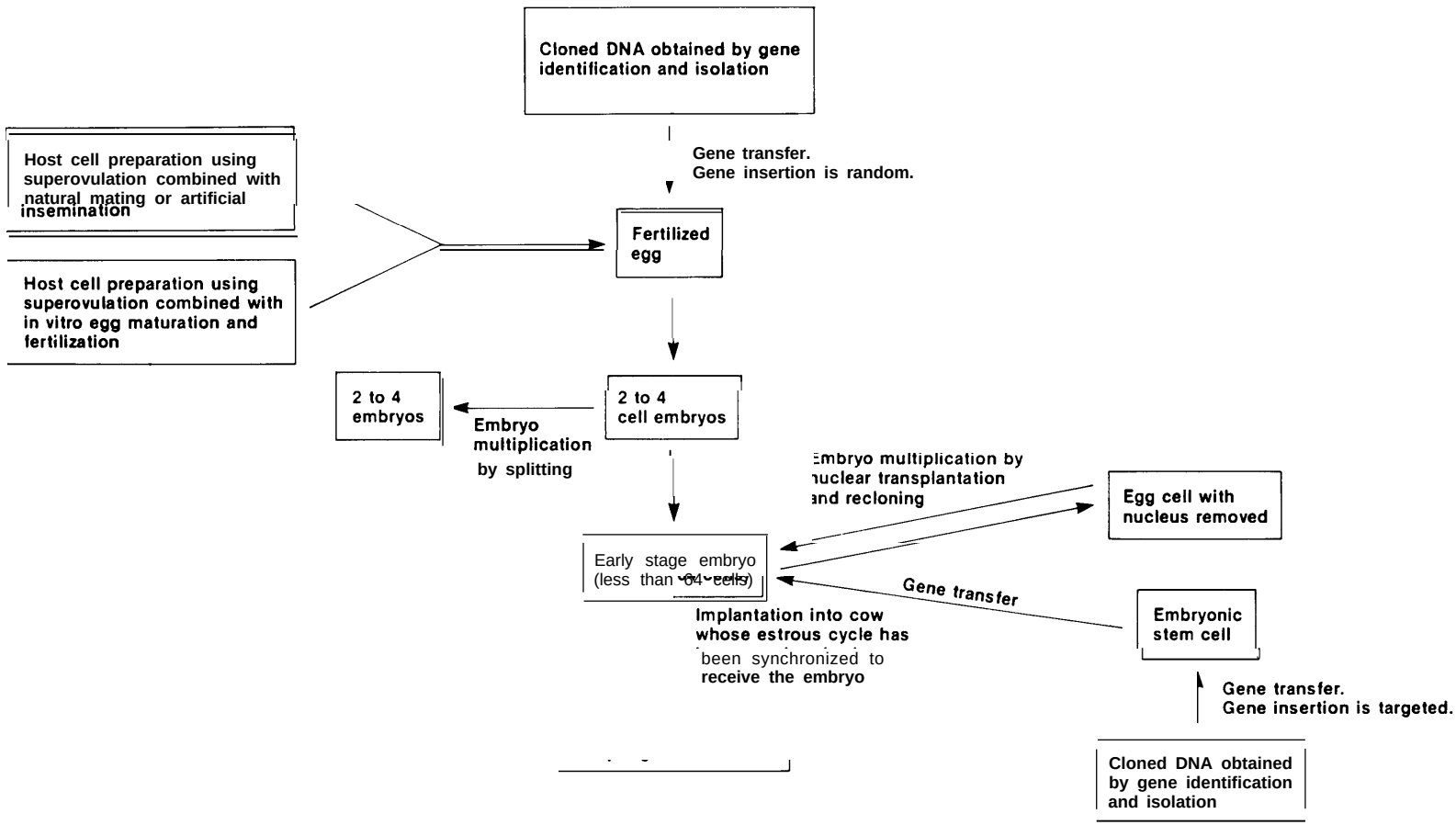
The process of making a transgenic organism is similar for plants and animals, and many of the tools and methodologies used are the same. As in plants, to create transgenic animals. the gene being transferred must first be identified and purified. Appropriate mechanisms (vector or nonvector) must then be found to transfer the gene into the animal cell, and appropriate regulatory sequences must be included to ensure proper expression of the gene. Unlike plant cells that are regenerated into whole plants by tissue culturing techniques, animal embryos (with the exception of fish) must be transferred to surrogate mothers for development and birth.

Gene Identification and Purification

The methods used to isolate and purify animal genes for transfer are the same as those used in plants, and have been described in detail in chapter 2. The method described in chapter 2 is the creation and screening of genomic libraries, libraries of DNA fragments that contain all of the genetic material of the chromosomes. An alternative approach is to create what is called a complementary DNA (cDNA) library. This method can also be used in plants, and it is frequently used in animals.

Genes are composed of DNA, and they code for proteins. But, before the protein is constructed, several intermediate steps occur. The DNA of the gene is first transcribed and processed into another compound called messenger ribonucleic acid (mRNA). It is the mRNA that serves as the actual template for the production of

Figure 3-3—Reproductive Technologies Used To Produce Transgenic Animals



SOURCE: Off Ice of Technology Assessment. adapted from J P Simons and R.B. Land, Transgenic *Livestock, J. Reprod Fert. Suppl. 34:237–250.* **1987**

proteins. Messenger RNA is not identical to the genomic DNA. This is because there are sequences of DNA contained within the gene that do not code for protein. After the DNA of the gene is transcribed to mRNA, these noncoding regions are snipped out and thrown away. Thus, the mRNA contains the coding regions, but not the noncoding regions of the genomic DNA.

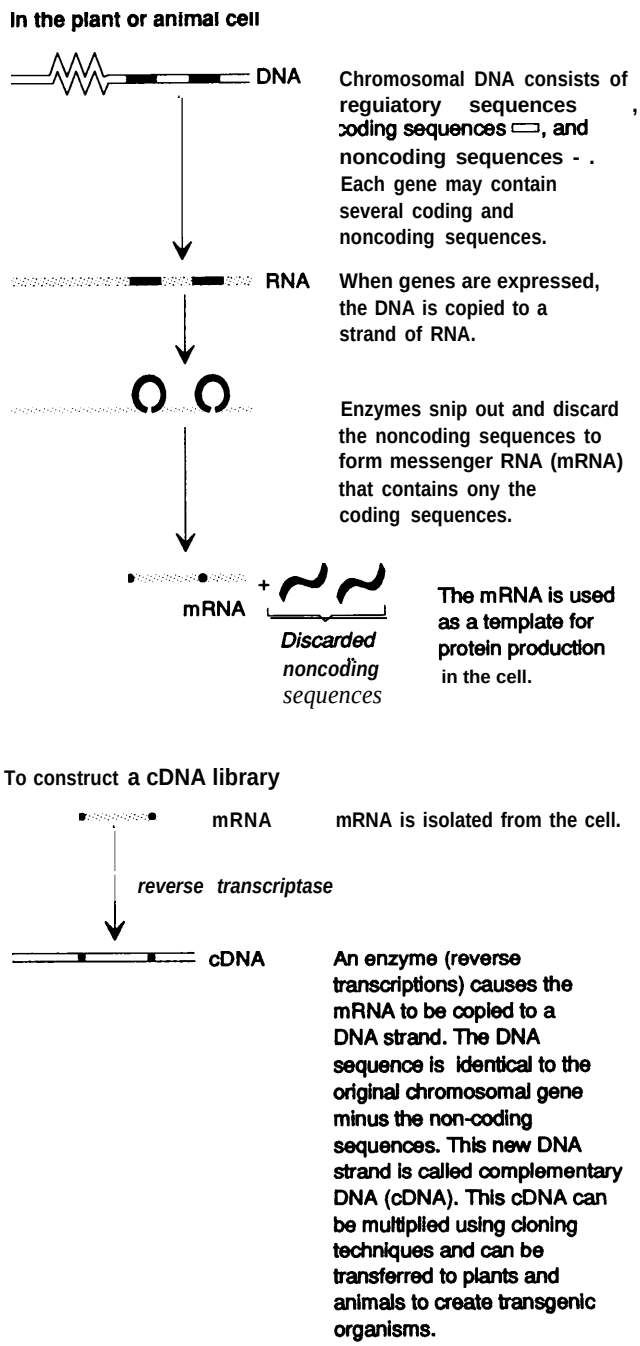
Special enzymes exist that can use the mRNA as a template to create DNA that has a complementary sequence to the mRNA. This new DNA is called complementary DNA (cDNA). It is identical to the sequence of the genomic DNA with the exception that, like the mRNA from which it was derived, it contains the protein coding regions, but not the noncoding regions of the genomic DNA (see figure 3-4). Thus. a library of cDNA sequences can be constructed from mRNA rather than the chromosomal DNA used to construct genomic libraries.

The mRNA that serves as the protein template for the desired gene can be obtained from tissues that express high levels of the protein. For example. if one wanted to find the gene that produces insulin, a reasonable approach would be to extract the mRNA from the pancreas, which produces very high levels of insulin. This high level of insulin production means that there is a significant amount of mRNA for insulin. Also, because the pancreas is specialized for insulin production, mRNA for other proteins, say for example, somatotropin, may not be present in large quantities. Thus, the use of cDNA libraries decreases the amount of genetic material that must be searched to identify the gene of interest. The process of looking for a particular gene is tantamount to looking for a needle in a haystack. Use of a cDNA library, as opposed to a genomic library, provides a smaller haystack that must be searched.

It might seem at first glance that the best method to use would be to construct cDNA libraries rather than genomic libraries. However, limits exist to the use of cDNA libraries. To construct both cDNA and genomic libraries, it is important to know the structure, sequence, and function of the protein for which one is trying to isolate the gene that codes for it. The lack of knowledge concerning the sequence and function of important proteins is the major constraint to the isolation and purification of the genes coding for those proteins.

Additionally, construction of a cDNA library is easiest when tissues exist in the organism that specialize in the high-level production of the protein coded for by the gene that is being isolated. This method does not offer significant advantages when the protein is produced in low quantities by nearly every cell in the organism.

Figure 3-4—Construction of a cDNA Library



SOURCE: Office of Technology Assessment, 1992

Also, evidence exists that genes that do not contain the noncoding regions do not function as well as genes that contain the noncoding sequences (5, 7, 33). While the functions of the noncoding sequences are not known

with certainty, they may play some role in the regulation and expression of the gene itself. Therefore, incorporating cDNA genes that do not contain the noncoding regions into transgenic animals results in the genes not being expressed as well as a genomic gene. Unfortunately, many of the animal genes that have been isolated and purified are cDNA genes rather than genomic genes. Thus, the tradeoff is that it may be easier to isolate and purify cDNA genes than genomic genes, but they don't work as well when used to create a transgenic organism (5, 7, 33).

Gene Transfer

Once an animal gene has been purified, it must be transferred to the host animal cell. Genes can be transferred using direct transfer methods (e.g., microinjection, electroporation, chemical) or vectors (i.e., viruses). The first transgenic animals created were mice in 1980 (37). Since then, transgenic cattle, sheep, swine, poultry, and fish have been produced.

The most common method used to produce transgenic animals is microinjection. This method involves directly injecting cloned DNA into a fertilized egg. [12] The cytoplasm of cow and pig embryos is opaque, and the embryos must first be centrifuged to locate the nucleus; otherwise the procedure for cows and pigs is similar to that **used** in mice, rabbits, and sheep (36). Fish embryos are surrounded by a tough membrane called a chorion, and this membrane first must be removed before DNA can be injected. Even with the removal of the chorion, the nuclei are not visible and so the DNA is injected into the cytoplasm. Injection into the cytoplasm rather than the nucleus requires greater amounts of DNA (34).

Other direct transfer methods attempted include the use of short electrical pulses (electroporation), or chemicals to make cell membranes permeable to the passage of large molecules **such** as DNA. These approaches have been used with sperm as well as eggs. The possibility of using sperm as a method to incorporate new genes into a species is an exciting prospect. One research group has reported using this method successfully to create transgenic mice that passed the new gene on to their offspring (27). Other researchers, however, have not yet been able to duplicate this result.

The use of electroporation methods in fish have resulted in up to 40 percent of the embryos becoming transgenic and this approach may be far more useful in fish than microinjection. Another approach being attempted in fish is the use of liposomes, vesicles contained in the phospholipid layer of cell membranes, as a means to encapsulate foreign DNA for entry into the cell. This method has not yet yielded any successes (34).

Poultry reproduction is significantly different from that of other livestock species. By the time the fertilized egg is layed, the developing embryo may already contain as many as 60,000 cells. This precludes using the microinjection technique because the number of cells that might incorporate the injected DNA could be small. Additionally, only some of the cells that incorporate the foreign DNA will express it. Attempts have been made to inject DNA directly into unfertilized eggs still in the ovary, **but** this method did not yield any transgenic offspring (24).

As a result of the deficiencies of direct gene transfer methods in poultry, a vector system has been developed. The most commonly used vector is a retrovirus. The gene that is to be transferred can be incorporated into the retrovirus. The host animal cell can then be infected with the retrovirus incorporating the new gene. Retroviruses are attractive vectors because only a single copy of the virus is integrated into a chromosomal site. Retroviruses also tend to be either species specific or to infect only a few closely related species.

Two types of retroviral vectors have been developed. Replication-competent retroviruses are those that are capable of self-replicating. These viruses have been successfully used in chickens. One-day-old embryos were infected with the retrovirus and transgenic chickens were hatched. Furthermore, the virus successfully infected germ line (sex) cells, and the new gene was passed on to the transgenic animals' offspring (24).

Replication-defective viruses lack the genes necessary for self-replication. These viruses cannot reproduce without the presence of a helper vector. The retrovirus is engineered in such a way that it contains all of the normal viral genes except those needed to package its own genetic material. The helper vector (also engineered) possesses the genes needed for packing retroviral genetic material, but does not include the other viral genes (i. e., genes that enable it to infect cells and cause virulence). Introduction of the retrovirus and the helper vector into host cells provides all of the elements needed to enable the retrovirus carrying the desired gene to infect and incorporate that gene into the host chromosomes. This method is considered safer than using replication-com-

[12] Specifically, the DNA is injected into the male pronucleus of the fertilized egg. The pronuclei are the egg and sperm nuclei present after the sperm penetrates the egg membrane.

petent ectroviruscs because the rcplictition-detective ectrovirus can only be infective and spread to other cells if the helper vector is present. However, there is a small possibility that the helper vector nd replicaton-defective retrovirus might recombine to form a replication-competent retrovirus. Additionally the DNA sequences carried by replication-defective retoviruses are not incorproated in the germ lnes of hickens. hence they are not passed to the offspring. Improved replication-defective retrovirus vectors are needed (2-I).

A number of transgenic cattle, pigs, sheep, chickens. and fish have been produced using direct transfer methods (almost exclusively microinjection) and viral vector methods. However, these techniques have several limi - tations. Microinjection techniques are expensive to use and the efficiency of transgenic animal production is very low. For a transgenic animal to be created. embryos must survive the physical manipulation and inflection of' DNA. must incorporate the DNA into their chromosomes, and must express the gene product. The percentage of microinjected embryos that actually results in transgenic animals is low, ranging, for example. from (). I to 4.45 percent in sheep and from 0.3 to 1.73 percent in swine (36. 38). The low rate of efficiency limits the study of transgenic livestock because of the high number of donor and recipient females that must be maintained tot- experimentation. Efficiency rates are much higher in fish, ranging from 35 to 80 percent, because fish undergo external fertilization and do not require in vitro culturing of the embryos and transfer to surrogate mothers.

Microinjection techniques are not only inefficient methods of creating transgenic animals. but they also do not provide any control over where the new gene is incorporated into the gernome (26). The site of gene incorporation is random. which also occurs with retroviruses. Because the site of incorporation influences gene expression, random insertion causes reduced control over the ability of researchers to control expression levels.

Because of these deficiencies. alternatives to viral vectors and microinjection are being sought. A promising new method for gcnerating transgenic animals has recently been developed in mice and may be applicable to other mammals. This new technique uses stern cells derived from an embryo. Stem cells are normally undifferentiated, that is. they do not become specialized tissue cells such as muscle, brain, liver cells, ect. Howe\'er. stem cells retain their ability to become specitilized cells under the proper stimuli (i.e., they are pluripotent). [13] Stem cells can be used as vectors to introduce selected genes into a host embryo. This method hits several significant advantages over microinjection methods. the most profound of which is that it is possible to insert DNA at specific, predetermined sites within the genomc of the stern cells (18). Targeted insertion is possible bccause stern cells have an intrinsic ability to recombine similar (homologous) DNA sequences. which results in the replacement of an endogenous gene with the desired gene. Stem cells can also be tested in vitro to ensure that integration of the new gene has occurred before these cells are transferred to a developing embryo.

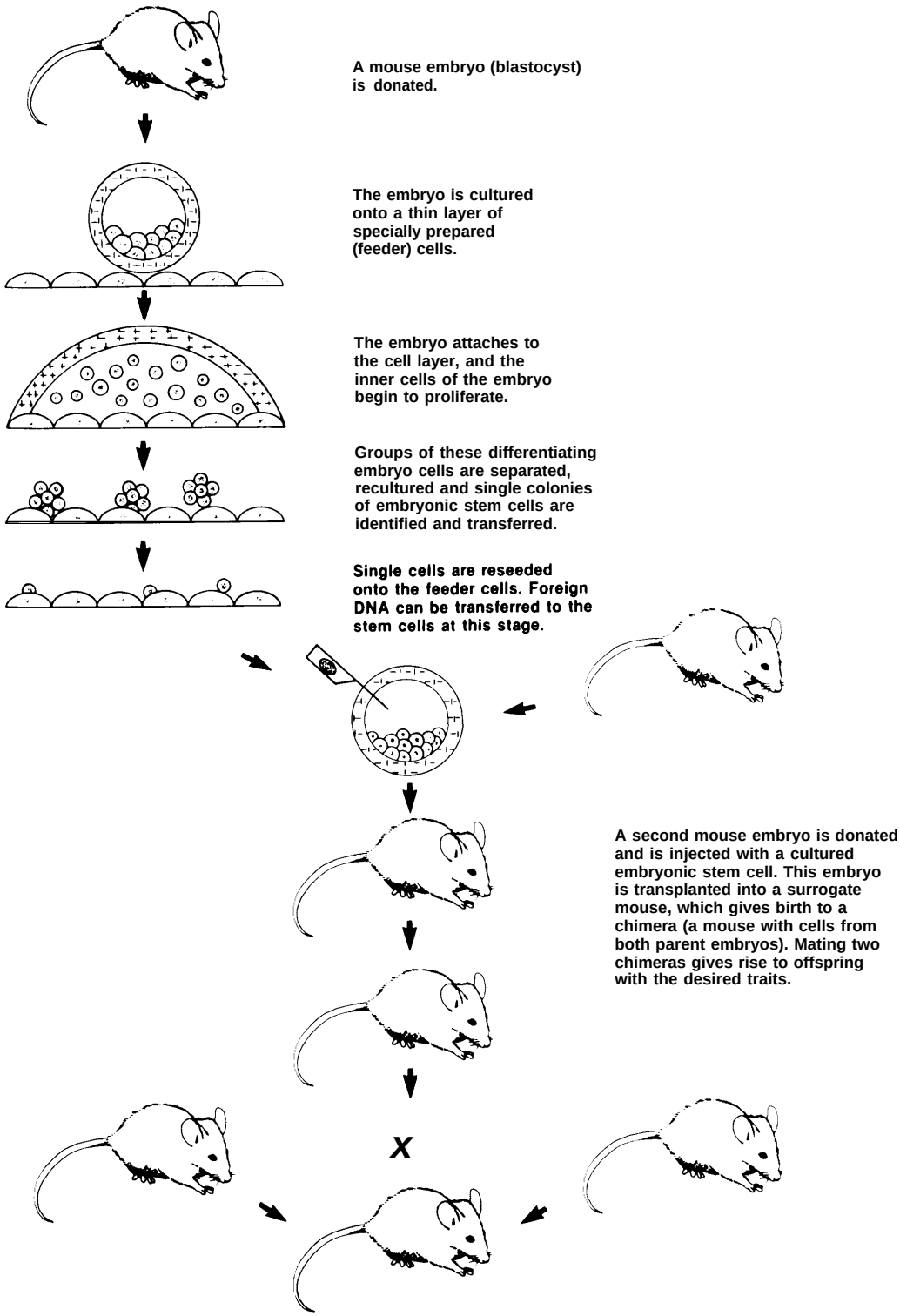
To isolate stem cells (see figure 3-5), an early stage embryo is cultured on a monolayer of specially prepared cells. The proliferating embryo cells are recultured until individual sterns cells can be isolated. These individual stem cells can then be cultured indefinitely. At this stage. DNA sequences containing desired genes can be inserted into the stem cells.[14] A geneticallly transformed stem cell is then microinjected into an immature embryo to produce a chimera, an organism that contains cells from more than one source. It the stem cells are incorporated into the germ lines of these chimeric animals, then these animals can be interbred to obtain offspring homozygous for the desired trait (18).

Use of the stem cell method will make it possible to produce a broad range of transgenic animals that could not be produced economically using direct microinjection or viral vectors. Targeted gene insertion also has the significant advantage of allowing host animal genes to be inactivated or removed and replaced with modified forms of the genes, such as ones that are expresses at a higher level, have new patterns of tissue-specific expression, or have a modified biological activity.

A host organism's endogenous genes can be inactivated by targeting an insertion into an essential region of the gene. This fact is of particular interest to the livestock industry, because inactivation of genes that have inhibitory physiological effects is likely to result in improvement in a number of productive traits. For example, bovine somatostatin is a hormone that inhibits bovine somatotropin production; inactivation of this gene would

[13] Pluripotency help make stem cells attractive vectors of DNA transfer. While in tissue culture, DNA can easily be inserted into stem cells. When stem cells are injected into an early stage embryo. the conditions for tissue specialization are present, and stem cells undergo the normal tissue development that occurs as the embryo develops during pregnancy. Thus. using stem cells provides an efficient means to transfer DNA.
[14] Methods used include viral infection and use of an electric pulse to make cell membranes leaky (electroporation).

Figure 3-5—Gene Transfer Using Embryo Stem Cell Culture



SOURCE: M.R. Capecchi, "The New **Mouse Genetics: Altering** the **Genome** by Gene Targeting," *Trends in Genetics 5:70–76, 1989*

result in increased endogenous somatotropin secretion and, presumably, increased milk production and more efficient growth. If successful, this technology could be used in lieu of administering bST exogenously to increase milk production. The genes controlling the production of inhibin, the ovarian hormone that reduces ovulation rate, provide another example of potential tin-gets for deactivation. The ability to inactivate genes also provides a powerful research tool for the study of the function of genes in vivo.

Stem cells have been isolated in mice and hamsters and possibly rabbits. There are reports that stem cells have also been isolated for swine (18). Progress is being made in isolating stem cells in sheep, and much research is being conducted to isolate bokvine stem cells, but to date, this has not been accomplished. There has been no documentation of embryonic stem cells being isolated from poulty ". However. in a similar type of procedure. 1-day-old embryonic cells from chickens have been isolated and introduced into immtaure embryos of other chickens. About I I percent of the resulting embryos were chimeric, and one embryo developed to hatching (24). Stern cells have not been isolated in fish (34).

Promotors and Gene Expression

The expression of new genes in transgenic animals is poorly regulated. Apprprate levels of gene expression are important. because overexpression can lead to impaired health in the transgenic animal. Better understanding is needed of how to turn genes on and off when desired; of how to regulate the level of gene expression: and of how to direct the expression of the gene to specific tissues at different stages of development. At the present time the factors that cause genes to have tissue and developmental specificity are not well understood.

Currently, fewer than 10 promotors or regulatory sefquences have been used to direct gene expression in transgenic live stock. Most of these promotors are derived from mice or viruses. The most commonly used promotor is the mouse metallothionein promoter, which is responsive to dietary stimulation by heavy metals such as zinc. Three promotors are being examined for their abilite to direct gene expression in mammary glands. A fourth promotor directs expression primarily to the liver.

It may be desirable to use promotors derved from the same species that is receiving the new gene. Evidencc euggests, for example, that using a mouse promotor sequence in pigs results in somewhat different gene expression than use of the same promotor in a mouse (18. 36).

Levels of gene expression do not aways correlate with the number of gene copies incorporated into the chromosome of a transgenic animal. This suggests that the site of the incorporate ion of the new gene in the host chromosome also affects gene expression. Given that embryonic stem cell procedures still require considerable development before directed insertion can occur. some researchers are examining methods to control gene expression independently of the site of integration. Research is focusing on regulatory elements that allow the new genes to provide their own environment for expression. [15]

Transgenic Poultry

Research emphasis has been given to improving growth and disease resistance. Bovine somatotropin has been transferred to chickens and increased the mass of the chicken. The envelope gene of avian leukemia virus has also been transferred to chickens and the cellss that expressed this gene have been shown to be resistant to subsequent infection with the same strain of vrirus (24).

Research is being conducted by USDA Agricultural Research Service and universities in the United States. as well as by a limited number of private firms. It is interesting to note that most of' the funding for transgenic poultry research conducted in the United States is being supplied by other countries (mainly Canada and France). Commercial availability will take 7 to 12 years after the production of an adequate number of transgenic fonder male chickens.

Transgenic Swine

Several genes have been successfully transferred into pigs, including those for somatotropin. human growth hormone releasing factor (hGRF). human insulin-like growth factor--l (hIGF-I), mouse MX (to investigate resistance to respiratory discuses), mouse whey acidic protein (WAP) (to investigate mammary- specific expression, and light and heavy beta chains for antibodies to produce specific immunoglobulns (36). With swine. as with other livestock species. researchers are focusing on improving growth. increasing disease resistance. and producing high-value pharmaceutical products.

[15] Such elements would function in a manner similar to that of dominant regulatory elements (DRE). When the injected DNA contains DREs, gene expression levels independent of the tissue and numbers of copies of the gene that was incorporated, were obtained. The "A-element," which seems to be a chromatin binding site, may permit genes to be expressed independently of the local environment into which they integrate (37).

Photo credit: U.S. Department *of* Agrculture, *Agricultural Research Service.*

Rooster on left was injected with genes of avian leukosis virus when it was a 1-day-old embryo. Roosters in center and on right are of two succeeding generations which directly inherited those virus genes.

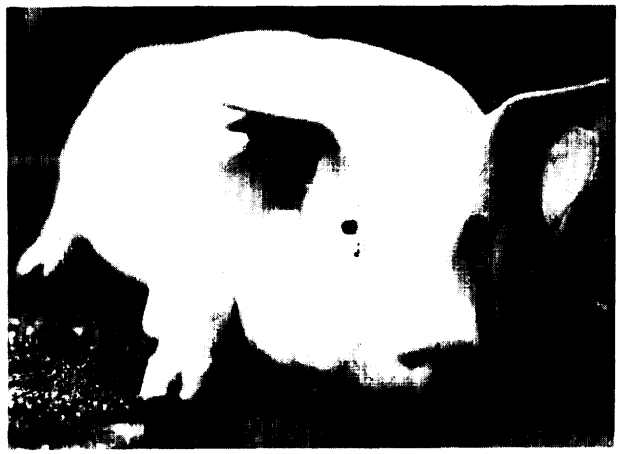


Photo credit: Mark Lyons

Transgenic pig at DNX research facility born with the capability to make human hemoglobin.

Somatotropin transferred to pigs has been shown to increase feed efficiency, enhance meat quality, reduce carcass fat, and increase the rate of gain. When fed a high-protein diet, transgenic pigs containing somatotropin genes gained weight nearly 17 percent taster than controls. and showed up to 18 percent greater feed efficiency. Backfat was significantly reduced and meat was leaner (36). Transgenic pigs that expressed the somatotropin gene passed that expression on to their offspring. Offspring that contain the somatotropin and who were fathered by boars that expressed the gene also expressed the sornatotropin gene. The offspring containing somatotropin genes who were sired by boars that did not express the somatotropin gene, also did not express the gene. This suggests that the stability and functioning of the gene are the same in the parent and offspring (36).

Pigs that continuously expressed high levels of somatotropin experienced significant health problems including lameness, susceptibility to stress. peptic ulcers, and reproductive problems. Animals that incorporated the somatotropin gene but did not express it, or that expressed it at low levels did not display these health problems (36).

Researchers are interested in improving disease resistance. Genes that confer resistance have not been isolated. Attempts to transfer genes that code for antibodies to compounds contained on the surface of selected bacteria and internal parasites are being made (28.51). Also, genes of the Class 1 Major Histocompatibility Complex [16] have been cloned. It may also be possible to induce immunity to specific viral diseases by transferring genes from the virus to the pig. This method has been used successfully in chickens and may also be applicable to other livestock species (36).

Attempts are being made to produce rare. medically important proteins in pigs. A U.S. firm (DNX) has announced that it has **successfully produced human hemoglobin in pigs. Transgenic swine research is** being conducted by the Agricultural Research Service, a few universities, and the private sector. The American Red Cross is also interested in the production of blood proteins in livestock. Commercial availability of transgenic pigs is not expected before the year 2000, and it is likely that the first transgenic pigs marketed will be used to produce pharmaceutical products. Additionally, pigs have a strikingly human-like physiology, and because of this, transgenic pigs are currently being developed to serve as a model system to understand and treat gastrointestinal cancers.

Transgenic Ruminants

The first transgenic ruminant to be successfully produced was a lamb, followed by goats and cattle. In cre-

[16] The major histocompatibility complex is a chromosomal region that contains several genes involved in regulating immune response.

ating transgenic ruminants. greatest research emphasis has been to improve growth characteristics (i. e., rate of weight gain, feed efficiency. and carcass composition). to produce valuable pharmaceutical products, and to enhance disease resistance.

Genes coding for somatotropin and somatotropin releasing factor (GRF) have been purified and transferred to sheep. While the genes have been successfully transferred and expressed. control of the level and timing of expression has not been achieved. Sormtotropin levels in sheep have varied from a low of 40 nanograms (ng)/ milliliter (ml) to over I ().000 rig/ml (31, 37). Extreme overexpression of somatotropin can lead to serious health problems in sheep. such as diabetes (39). In the future, researchers would like to alter the composition of milk and meat for improved processing characteristics, for higher nutrition. for less fat. and to alter the types of fat contained.

Another major research area involves transferring genes that code for the production of valuable pharmaceuticals. Production of blood clotting factors (factors VIII and 1X), tissue plasminogen activator (TPA. used to dissolve blood clots that cause heart attacks), erythropoietin (used to treat bone marrow side effects resulting from AIDS treatment). and o-l-antitrypsin (AAT. used to treat emphysema are being investagated. A U.S. firm (Genzyme). in conjunction with Tufts University. has successfully produced TPA in goats (13.14). A Scottish firm (Pharmaceutical Prteins. Inc) has produced AAT in sheep. and is conducting research to produce Factors VII and IX and crythropoietin (30. 52). Transgenic cows producing high levels of pharmaceuticals in their milk have not yet been reported, but these animals are under development in a number of public and private laboratories. For example. a joint U.S. and Dutch group (GenPharm International. Gene Pharming Europe BV, and two Dutch Universities) has successfully produced tramsgenic cattle incorporating the human lactoferrin (which has antibiotic propertics) gene in the genome (25).

Attempts tire being made to identify promotors that espress gene products only in milk. Research is being conducted on whey acid protein. a protein only found in milk. to identify the promotor that directs the synthesis of' this protein. The goat (3-cascin promotor is also being used (14). Once appropriate promotors are found. the high levels of U.S. milk production coupled with the ease of milk collection may make this production method more cost effectove than the cell culture systems currently used in the production of certain pharmaceutical proteins.

Enhanced disease resistance is another focus of research. Diseases that may be potentially controlled by the production of transgenic organisms include progressive pneumonia in sheep. and caprine arthritis-encephalitis in goats. The introduction of preformed antibodies have been shown to provide resistance to specific infections in mice and the antibody gene antiphosphoryrlcholine has been inserted in sheep (28). Researchers are also attempting to insert viral envelope genes that could possibly lead to enhanced resistance to viral infections.

Researchers in Australia are attempting to increase wool production in sheep. Currently, wool production is limited by the amount of cysteine contained in and absorbed from the diet. Researchers are transferring bacterial genes that code for enzymes that produce cysteinc from sulfur in the diet (37).

Research to produce transgenic ruminants is limited due to the high cost of' the research. Research is conducted primarily in the United States by the Agricultural Research Service. a handful of universities. and a few private sector firms. and in Austrulia, Great Britain, and the Netherlands. It is not expected that transgenic ruminants will be commercially available before the turn of the century.

Transgenic Fish

Several species of transgenic fish have been produced. including rainbow trout, salmon, common carp. loach. catfish, tilapia, goldfish, zebrafish. and medaka. Several genes have been transferred to fish. including human. bovine, and trout somatotropin; genes that confer antibiotic resistance; and fish antifreeze protein genes (34).

Transgenic fish containing the trout somatotropin gene grew 22 percent more than controls. and transmitted this increased growth rate to their offspring (34). Some species of fish produce a novel set of proteins that allow them to withstand extremely cold water without freezing. These antifreeze proteins are produced year round by fish living in polar regions, and during the winter in fish living in temperate regions. The antifreeze genes in several species have been purified. Antifreeze protein genes from winter flounder have been transferred to salmon. Expres- s ion levels of the gene were low. however. and protection against freezing was not achicved (34).

Research Needs

While significant advances in transgenic animal production have been made, it is unlikely that transgenic animals will be commercially available before the end

Photo credit: Thomas Chen, University of Maryland

Resultant transgenic carp with trout somatotropin incorporated into some but not all of their cells. The PI (middle) and F1 (top) transgenic carp are on average, 22 percent larger than their nontransgenic siblings (bottom).

of the 1990s at the earliest. The ability to produce transgenic livestock possessing traits of economic value is currently limited by the absence of embryo stem cell technology, the lack of appropriate gene expression promotors, and the lack of knowledge about the physiological consequences of specific gene expressions. While the techniques for isolating and sequencing animal genes are relatively well developed, understanding of the functions of the genes has lagged. Analysis of gene function is complicated by the fact that many traits are controlled by multiple genes. Thus, manipulation of such traits will require detailed understanding of these genes and of their interactions. Ultimately, identification and understanding the physiology of the major genes controlling growth and lactation, reproduction, and disease and stress resistance in animals is needed. An active genome mapping program could enhance these developments.

ANIMAL HEALTH TECHNOLOGIES

Improvements in animal health will provide considerable cost savings to the livestock industry. Biotechnology is rapidly acquiring a prominent place in veterinary medical research. New vaccines and diagnostic kits are being developed to detect and prevent a variety of major livestock diseases.

Vaccines

Vaccines are agents that stimulate an effective immune response without causing disease. Traditional methods of vaccine development have involved killing or modifying pathogenic organisms to reduce the potential for disease while preserving that pathogens' ability to induce an immune response. Biotechnology is being used to create new vaccines. Approaches used include deleting or inactivating the genes in a pathogen that cause disease, and inserting into a vector genes that cause an immune response to a pathogen. Synthetic peptides are also being produced that stimulate the immune response.

Gene Deletion Vaccines

Gene deletion techniques have been used to develop both viral and bacterial vaccines. The first gene deletion viral vaccine to be approved and released for commercial use was the pseudorabies virus vaccine for swine. initially, the removal of a single gene reduced the virulence of the virus. Since then, other genes have been deleted with a continuing reduction of virulence. Chickens that have been inoculated with recombinant avian leukosis virus (ALV) developed antibodies to the virus without developing the disease. Methods to decrease the virulity of live viruses lead to more effective vaccines because live virus vaccines stimulate the immune response more effectively than do killed virus vaccines (32).

Bacterial vaccines have also been produced. Esche*richia coli* that lack certain genes. for example, have been shown to provide protection against gram-negative bacterial infections in cattle and swine. Live Salmonella modified to prevent reproduction in vivo have also proven to be an effective vaccine for cattle (32).

Most gene deletion viral vaccines will not be available before 1995 with the exception of the pseudorabies vaccine, which is already available, and possibly the rabies and rinderpest vaccines, which are currently undergoing field trials.

Photo credit U.S. Department of Agriculture, Agricultral Research Service

Molecular biologists analyze DNA sequence reactions of a gene detection vaccine made from a modified bacterium.

Vectored Vaccines

New vaccines are also being created using vectors. Development involves deleting disease-causing genes from the vector if it is a pathogenic organism, or using a nonpathogenic vector. Genes that code for protective antigens produced by pathogens can be inserted into a vector. Inoculation of the animal with the recombinant vector stimulates an immune response to the inserted genes and confers protection against the pathogen. Pathogen surface protein genes are most commonly inserted into the vector. Inoculation of the animal stimulates production of antibodies to these surface proteins. When an animal is infected with the pathogen, it already recognizes that pathogen and produces antibodies against it. As an example, recombinant vaccines have been developed against the coat protein of a bacterial pathogen of the genus *Vibrio,* in fish.

The most commonly used vector is the *Vaccinia* virus. *Vaccinia* viruses are used because they are easy and relatively cheap to manufacture, large enough to accommodate the insertion of many new genes (1). and stable without refrigeration. A single inoculation can induce immunity, and the recipient produces the bulk of the vaccine, eliminating the need for large vaccine factories. *Vaccinia* viruses also stimulate more than one type of immune response (i. e., they stimulate both B and T lymphocytes). However, there are disadvantages to using vaccinia virises: they have a wide host range (including humans), and could infect species other than target species; it is possible that they can revert to a virulent form; they cannot be administered orally; and they may pose a risk to immunosuppressed recipients. *Vaccinia* hosts have been used to produce vaccines against rinderpest (cattle), rift valley fever (sheep), Venezuelan equine encephalitis, bovine leukemia, rabies (cattle). vesicular stomatitis (cattle), avian influenza, avian infectious bronchitis, and respiratory syncytial disease (1, 32).

Fowlpox virus is also being used as a vaccine vector. This virus cannot replicate in humans and is being used as a carrier for genes of pathogens that cause the poultry diseases of Newcastle disease, Marek's disease, bursal disease, coccidiosis, avian influenza, and avian infectious bronchitis. Raccoon poxvirus is being developed as a carrier for rabies. In fish, vaccines to control infectious haematopoietic necrosis virus (IHNV), a devastating viral disease of trout and salmon, are being developed by inserting coat protein genes into vectors. Other genetically engineered virus vectors that are in the early stages of development include avirulent adenoviruses, herpesviruses, murine and avian retroviruses, and bovine papillomavirus (1, 32).

Bacterial vectors are also being developed. *Escherichia coli* and *Bacillus subtilis* are being used to produce antigenic proteins. They can be used to produce antibodies to *Theileria annulata* (a tick-borne parasite of cattle and sheep), coccidia in poultry, anaplasma (a parasite of cattle), and cysticercosis (a tapeworm in ruminants and swine). Pili genes from Bacteroides nodosus, the cause of foot rot in sheep, have been cloned into *Pseudomonas aeruginosa,* and have been shown to be an effective vaccine for foot rot (1, 32).

Natural and Synthetic Peptides

A number of animal species are known to produce small peptides associated with white blood cells and that are effective in destroying bacteria, fungi, and enveloped viruses. Such peptides, referred to as antimicrobial peptides, include defensins in mammals, bovine nubopeptides in cattle, magainins from frogs, and cecropins from moths. Some of the smaller peptides have been synthe-

sized and appear to have biologic activity similar to that of the natural peptides, and could be used in a manner similar to antibiotics. The genetically engineered protein lysostaphin, which kills *Staphylococcus aureus,* has reportedly achieved cure rates as high as 80 percent for mastitis in some clinical trials (1). Commercial development will take 5 to 10 years.

Synthetic peptides can be constructed to stimulate an immune response in animals. Small fragments of proteins that are homologous to proteins coded for by the foot and mouth disease virus have been used to stimulate an immune response to that disease in cattle and pigs. Synthetic peptides have been **used to inhibit critical functions of lentiviruses in** sheep. Administration of a viral surface protein elicited production of an antibody and provided protection in fish. Commercial availability is not likely until the end of the decade.

Monoclinal Antibodies To Confer Passive Immunity

Monoclinal antibodies can be used to provide passive immunity to disease-causing microorganisms. They generally act not by stimulating the immune response of the animal itself, but rather by providing exogenous antibodies to the pathogen. Because monoclinal antibodies are specific to one antigen, they may provide only weak immunity to pathogens that have more than one immunogenic region of their surfaces.

Certain strains of the bacteria *Escherichia coli* cause diarrhea in newborn calves. For diarrhea to occur, the bacteria must attach to the walls of the intestines. Attachments occur via cilia-like projections, called pili, that cover the surface of the bacteria. Monoclinal antibodies specific to the attachment proteins on the pili prevent attachment of the bacteria to the intestinal wall and prevent calves from getting diarrhea. A product currently on the market for diarrhea prevention in calves is Genecol-99 (50). Monoclinal antibodies specific for bluetongue also have been shown to protect sheep from this virus in trials.

In addition to monoclonal antibodies, antisense agents can also provide passive immunity. Antisense agents can be synthesized and used as drugs, or used to block viral genes. They are very sensitive, but are susceptible to enzymatic degradation A delivery is a problem (I).

Immunomodulators

Immunomodulators are hormone-like molecules that play a role in coordinating immune defenses to infectious agents, cancer, and autoimmune diseases. They act to boost or accentuate the immune response. Some of these molecules, the lymphokines, for example, are produced by white blood cells. Other immunomodulators, the cytokines, for example, are produced by other body cells. Two classes of lymphokines, the interleukins and the interferon, have been the focus of research attention.

Interleukins are compounds that transmit signals between white blood cells. These signals help to stimulate the proliferation of disease-fighting white blood cells and the production of antibodies. Interferon induce the expression of class 11 histocompatibility antigens (define) and enhance their activity.

Several interleukins and interferon have been identified in mammals, and the genes encoding some of these compounds have been isolated and cloned into bacteria (e.g., bovine alpha, beta and gamma interferon, bovine interleukin-2) (32). Lymphokines are being tested as adjuvants to boost immune responses to poorly immunogenic vaccines. For example, interleukin genes and genes for compounds that cause immune responses in animals (antigens) are being inserted together into viral or bacterial vaccines. This combination may enhance the immune response of the animal and lead to increased protection against the antigen.

Recombinant interleukins produced in bacteria or other expression vectors may also be used therapeutically to assist in overcoming certain infections. For example, recombinantly produced interleukin-2 is being tested as a control for shipping fever and mastitis in cows. Mechanisms by which these regulatory proteins modulate immune response are now being investigated in domestic animals. Biotechnology is being used to identify and repilicate these compounds so that their function can be investigated.

Diagnostics

Safe, accurate, rapid, inexpensive, and easy-to-use diagnostic procedures are critical to the livestock industry at virtually all points in the production process. Examples of diagnostic tests include pregnancy tests and assays for pathogenic organisms. Many currently used diagnostic tests are costly, time consuming. and labor intensive, and some still require the use of aninml assay systems. Monoclinal antibodies and nucleic acid hybridization probes can be used to produce simpler, easily automated. and highly sensitive and specific diagnostic procedures.

Antibodies are proteins produced by the body in response to foreign chemical substances. Monoclonal antibodies are produced by a cell line expressing only a single antibody type. They are the primary tools for bio-

technology-based diagnostics. At least 15 different rapid diagnostic tests based on monoclinal antibodies are on the market or will be soon (table 3-4). These tests are highly specific and most lend themselves to automation, potentially allowing their application in mass screening systems for disease surveillance and control. Some of the tests have been adapted to field use and can be used by veterinarians or producers. The rapid commercialization of these products is having a significant impact on animal health management and disease control.

Monoclinal antibodies are also being used in enzyme-linked-immunoabsorbent-assay (ELISA) systems to provide sensitive, quantitative blood assays of toxins, hormones, chemicals (e. g., pesticide and antibiotic residues), and a variety of antigens including microbial agents. Many of these tests are commercially available. In some instances monoclinal antibody diagnostics have been used to replace bioassays such as mouse inoculation tests.

The high specificity of monoclinal antibodies has generally been felt to make them less useful than polyclonal antibodies in initial screenings for diseases that have many serotypes. However, an ELISA kit containing just two monoclinal antibodies was able to detect 800 different *Salmonella* strains, so it may be possible that diagnostic kits containing just a few monoclinal antibodies could be useful for initial screening of pathogens (l).

Nucleic acid hybridization can also be used to diagnose the presence of microbes and parasites (table 3-5). Such assays rely on the bonding of a specific DNA or RNA segments (the probe) to complementary RNA or DNA fragments in a test sample. The probe is attached to (labeled by) a radioactive compound or to a color compound to allow for detection. DNA probes are most commen. The development of RNA probes is very recent, and they are used to detect RNA viruses.

The major limitation of nucleic acid hybridization is inadequate signal strength. The amount of target nucleic acid present in some samples may be too small to emit a signal the probe can detect. The polymerase chain reaction technique (PCR) (see ch. 2) can be used to amplify the amount of target DNA present and improve the ability of the probe to detect its presence. Similarly, bacteriophage replicase systems can be used to amplify the RNA present in a sample.

Currently, the most reliable probes are those that are radioactively labeled. Use of these probes requires expensive equipment and trained technicians. thus precluding their use in the field. Alternative calorimetric techniques currently in development will replace the radioactively labeled probes and make the use of this technology more commercially attractive (32).

The advantage that nucleic acid probes have over traditional diagnostic techniques is speed. Conventional tests for anaplasmosis and Johne's disease (an intestinal disease in ruminants), for example, require about 6 and 14

Table 3-4—Diagnostic Monoclinal Antibody Kits

Avian leukosis
Avian reovirus
Bluetongue
Bovine virus diarrhea
Canine parvovirus
Coccidiosis
Episotic hemorrhagic disease
Equine infectious anemia
Feline infectious peritonitis
Feline leukemia[a]
Feline T-lymphotropic lentivirus
Feline T-lymphotropic lentivirus (Feline leukemia
Mastitis
Pseudorabies[a]
Rotavirus gastroenteritis
Trichinosis

[a]More than one company has a kit on the market

SOURCE: Office of Technology Assessment, 1992.

Table 3-5—Pathogens for Which Diagnostic Kits Using Nucleic Acid Probes Are Available

Viruses
Bluetongue
Bovine coronavirus
Bovine leukosls
Bovine virus diarrhea
Equine encephalosis
Foot and mouth disease
Infectious bovine rhinotracheitis
Porcine coronavirus
Porcine parvovirus
Rabies
Rotavirus
Bacteria
Anaplasma marginale
Campy lobacter
Enterotoxigenic Escherichia coli
Leptospira
Mycobacterium
Mycoplasma
Salmonella
Shigella
Parasites
Babesia bovis
Eimeria tenella
Eperythrozoon suis
Hammondia hammondi
Theileria parva
Toxoplasma gondii
Tritrichomonas foetus
Trypanosoma brucei brucei
Trypanosoma congolense

SOURCE: Office of Technology Assessment, 1992.

weeks, respectively, to confirm the presence of the pathogen. This much time allows for interim spread of disease. With DNA probes the presence of these pathogens can be confirmed within a few hours.

Restriction Fragment Length Polymorphism maps (RFLPs) can also be used for diagnostic purposes. This procedure has been used to distinguish different strains of African swine fever virus and has shown that equine herpesvirus- 1 can infect and cause abortion in cows under natural conditions.

Research to develop diagnostic kits using biotechnology is being conducted in both the private and public sector. Currently, several diagnostics kits are commercially available. Development time to bring new diagnostic kits to market ranges from 2 to 5 years. Generally, less time is required to develop monoclinal antibody kits than nucleic acid probes.

FOOD PROCESSING APPLICATIONS

The processing of animal products into foods also will be affected by biotechnology developments. Americans consume many meat and dairy products that are fermented; genetically engineered fermentation starter cultures are being developed for these products.

Starter cultures are living microorganisms used to produce fermented products such as cheese, yogurt, butter, buttermilk, sour cream, salami, and sausages. Culture organisms have been safely consumed by humans for centuries and serve as ideal hosts for the production of these natural foods. The metabolic properties of these organisms directly affect the properties of the food product, including flavor and nutritional content. In order to improve various properties of food products, food microbiologists attempt to manipulate the traits of the microorganisms, primarily through mutation and selection. The cloning and gene transfer systems developed in the 1980s are being used to construct strains with improved metabolic properties more rapidly and precisely than is possible with traditional methods. The development in this decade of new strains with precise biochemical traits will have an impact on several aspects of fermentation, including production economics, shelf-life, safety, nutritional content, consumer acceptance, and waste management (19).

Although much of the current work to develop new strains of microorganisms has focused on the use of E. *coli* and other nonfood microorganisms, there are distinct advantages to engineering starter cultures for producing high-value foods. For example, construction of cultures resistant to attack by viral infection will impact processing costs by eliminating waste. Cloning of the genes responsible for ripening of aged cheeses can decrease storage costs by accelerating ripening. Production of natural preservatives, such as nisin (effective in inhibiting foodborne pathogens and spoilage organisms), will help ensure the safety and extend the shelf life of fermented meat and dairy products. Starter strains engineered to mimic the function of nitrates could reduce the use of these compounds in cured meats.

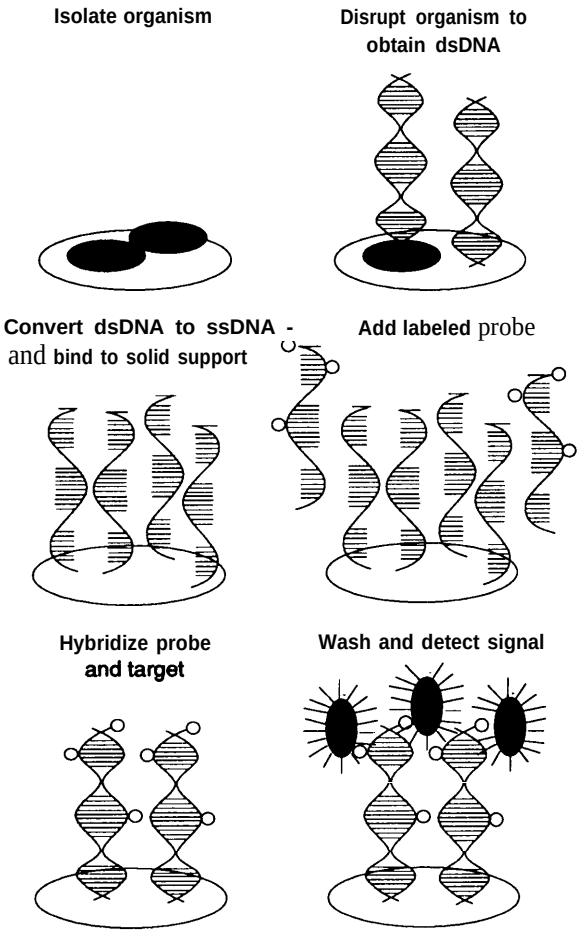
Cloning of the gene(s) responsible for enzymatic reduction of cholesterol or modification of the degree of saturation of meat and milk fat will improve the nutritional quality of fermented products. The ability to engineer strains capable of producing enhanced flavors or natural stabilizers will influence consumer acceptance of fermented dairy foods. Enzymes, which are added to the curd to accelerate ripening, or to produce dairy products acceptable for digestion by lactose-intolerant individuals, will also be produced more economically by engineered microorganisms (19).

A genetically engineered version of the enzyme preparation rennet, which is normally extracted from the forestomach of calves, has recently been approved by FDA for use in cheese manufacturing (See ch. 10).

Processing of animal products generates many wastes such as blood, bone, collagen, shells, fish parts, and milk whey. Bacteria and yeast strains engineered to convert these waste products into useful products could decrease the cost and problems associated with their disposal. For example, engineered yeast strains are capable of fermenting the lactose in whey to value-added products, such as vitamin C, biofuels such as ethanol and methanol, or pharmaceuticals. Whey protein could potentially be used to produce specialty chemicals with biotechnology.

Biotechnology products can be used to monitor animal products for food safety. DNA probes and monoclinal antibodies can be used to analyze raw materials, ingredients, and finished products for pathogenic organisms, bacterial or fungal toxins, chemical contaminants (i.e., pesticides, heavy metals), and biological contaminants (i.e., hormones, enzymes) (figure 3-6). Detection kits are commercially available. For example, kits are available to monitor several pesticides and antibiotics. Kits are also available to detect Salmonella. Animal cell cultures may partially replace whole animal systems to test for acute toxicity. Biosensors may be used to monitor food processing, packaging, transportation, and storage (19).

Figure 3-6—Basic Steps in a DNA-Probe Hybridization Assay



Organisms present in a food product are trapped on filters and disrupted to obtain double-stranded DNA. Following denaturation of the DNA to single strands, the labeled probe is allowed to hybridize with target DNA. Hybridization can be detected by a number of methods.

SOURCE: *Journal of Food Protection 54(4):387–401, 1991*

SUMMARY

Biotechnology will offer many new opportunities to alter the manner in which livestock is produced in the United States. New products are being developed to enhance feed efficiency, improve livestock reproductive performance, and enhance herd health management. Producers, food processors, and consumers all potentially may benefit from these new products.

Several new products are under development to enhance the feed efficiency and growth of meat-producing animals, and to increase milk yields in lactating animals. Increased feed efficiency could significantly decrease the cost of producing livestock. New growth promotants result in meat that is far leaner than that which is produced naturally, a benefit to consumers who desire less fat in their diets. Three new products (bST, pST, and beta-agonists) currently are undergoing FDA review for use in livestock production. Additionally, traditional growth promotants, such as steroids and antimicrobial agents, continue to be improved.

New reproductive technologies offer producers the opportunity to rapidly upgrade herd quality by selecting and incorporating desired traits at a faster rate than could be accomplished with traditional breeding. It is now possible to induce superior females to shed large numbers of eggs, and then to fertilize those eggs in vitro with the sperm of superior males. The embryos may be implanted into surrogate mothers whose estrus cycle has been synchronized to accept the embryo. Cloned embryos are currently marketed, and more efficient methods of embryo production are being developed. Advances in embryo and sperm sexing will allow livestock producers to choose the sex of the progeny and to breed for animals of highest value (e. g., females in dairy, males in beef production).

Eventually, transgenic livestock will be commercially available. Efforts are under way to produce transgenic livestock with improved production characteristics such as enhanced disease resistance, leaner carcasses. and faster growth. However, the first transgenic livestock will most likely be animals that produce high-value pharmaceuticals in their milk. Several firms have successfully produced such transgenic animals; however, commercialization is not likely to occur before the end of this decade.

New vaccines, therapeutics, and diagnostic kits will improve the ability of livestock producers to manage herd health. Several vaccines and diagnostic kits are commercially available, and more are under development.

The food processing industry will also be affected. New enzymes and starter cultures for cheese and dairy manufacturing, and meat processing are being produced with biotechnology. One genetically modified enzyme preparation, chymosin. has been approved as generally regarded as safe (GRAS) by FDA for use in cheese making. Biotechnology can be used to improve the safety of food products through the development of nucleic acid probes and monoclinal antibodies to detect the presence of microorganisms, chemicals, heavy metals, and other contaminants in food products. Additionally, new methods to manage processing waste products. such as whey, are under development.

Despite the potential opportunities offered by biotechnology, these technologies are not without controversy. Concerns have been raised about the effects of these technologies on farm survival and structure, food safety, animal welfare, and the environment. Additionally, many of these technologies will place a premium on farm management skills, and thus may not be appropriate for all farmers. These issues are discussed in more detail in the following chapters.

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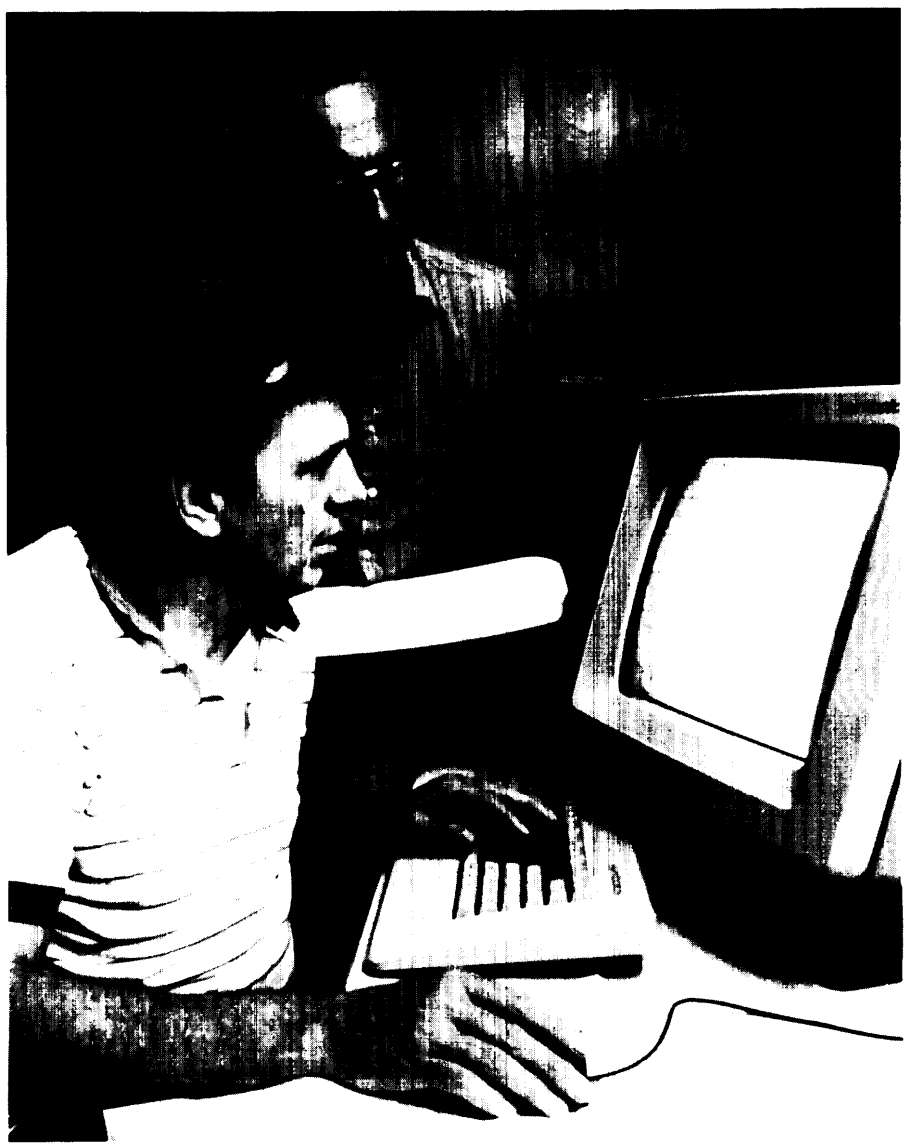
Chapter 4

Advanced Computer Technology



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Advanced Computer Technologies

INTRODUCTION

Since the industrial revolution, agricultural systems have intensified, and agricultural productivity has significantly increased along with farm size. Labor-saving devices on farms have increased output per worker several-fold. and advances in understanding and application of biological principles have significantly boosted agricultural yields. With greater production per acre and animal, however, farm management becomes correspondingly more challenging and complex. In general, methods for making management decisions have failed to meet this challenge. As a result, many decisions are ‘‘ uninformed” and many agricultural systems poorly managed.

The application of advanced computer technologies to agricultural management can help remedy this situation. improved access to information will allow farmers to more effectively monitor progress toward optimal performance. Computer technologies of potential use to agricultural managers are advancing at a tremendous rate. The performance of computers has increased several-fold with each new generation of computer chip (figures 4-1 and 4-2). In the last decade. microcomputers have evolved from 64-kilobyte machines with a 320-kilobyte floppy drive to machines with several megabytes of memory and several hundred megabytes of permanent storage; such machines approach the performance of mainframe computers (25 , 54) and can store massive amounts of information.

Advances are also occurring in software technologies, allowing improved utilization of stored information. Decision support systems, for example, provide enterprise-specific, expert recommendations to decisionmakers. Several other types of information technologies allow for rapid access to the latest information.

These advances will provide the tools to improve farm management. For example. close monitoring of” animal performance will allow early detection of diseases and can help reduce stress in animals. Overall, advanced computer technologies can provide managers with the ability to systematically determine the best decision rather than arrive at decisions in an ad hoc fashion. Optimal decisionmaking requires a holistic view of a farm enterprise, factors that affect it, and the probable consequences of management decisions. Thus, a farmer deciding whether to plant a specific crop on a specific field should weigh the profitability of the crop as well as overall farm needs (i. e., nutrition requirements if it is an animal enterprise). The decision will impact land sustainability and the need to use certain pesticides and herbicides or other pest-control methodologies. Computer technologies, by providing the capability of taking these multiple factors into account, can help producers arrive at the best possible decisions and management strategies.

The quality of management, in turn, will influence productivity as well as the future impact of some biotechnologies. For example, the response of milk cows to bST is directly related to management. Poorly managed dairy herds have a lower response to bST than well-managed herds (figure 4-3).

SPECIFIC COMPUTER TECHNOLOGIES

Computer technology is changing at an unprecedented rate on three different fronts, causing a "three-dimensional" information revolution. Rapid advancements in traditional database and computational programs: in symbolic computing and artificial intelligence: and in systems that improve access to information constitute the three dimensions of the information revolution.

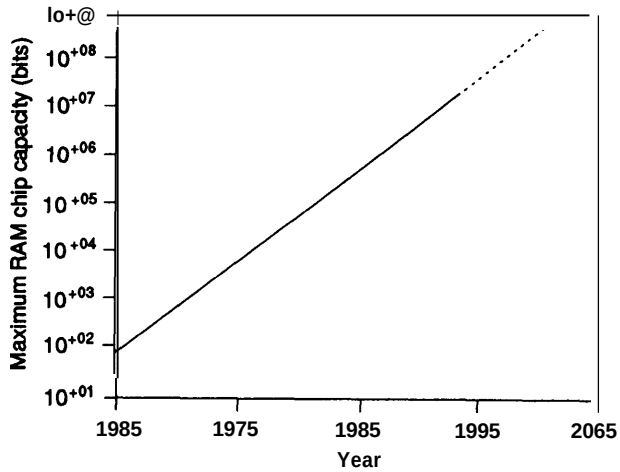
Knowledge-Based Systems

Traditional database and computational programs, which are largely numeric and follow established algorithms. are invaluable resources, but they cannot easily deal with symbolic data or mimic an expert’s reasoning process. The so-called knowledge-based systems in the category of symbolic computing and artificial intelligence have these capabilities. American agriculture is just now beginning to capitalize on these resources.

Essentially, knowledge-based systems present expert knowledge in a form that can be used to solve problems. In addition to expert knowledge, such systems require situation-specific databases. For systems that operate in real-time, sensors may play an important part in collecting data for knowledge-based systems (40). General **uses** of knowledge-based systems include:

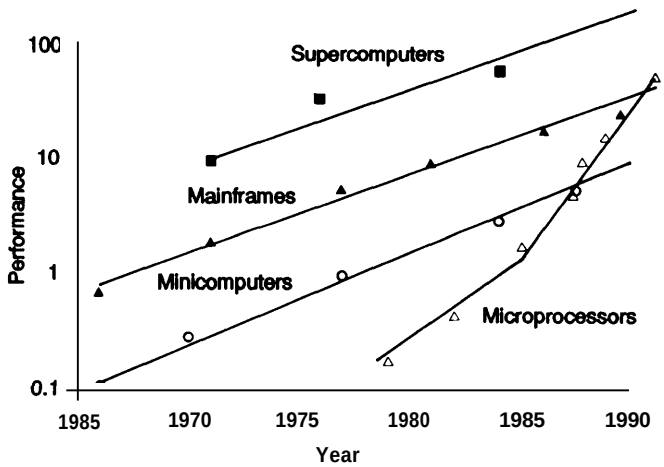
1. recommending solutions for problems (e. g., diagnosis),
2. monitoring the status of a system to determine significant deviations (i. e.. management-by-exception). and

Figure 4-l—Trends in Semiconductor RAM Density



SOURCE: J L Hennessy and N P Jouppi, Computer Technology and Architecture: An Evolving Interaction, ' *IEEE Computer* September:18. 1991

Figure 4-2—Trends in Microprocessor and 'Mainframe CPU Performance Growth



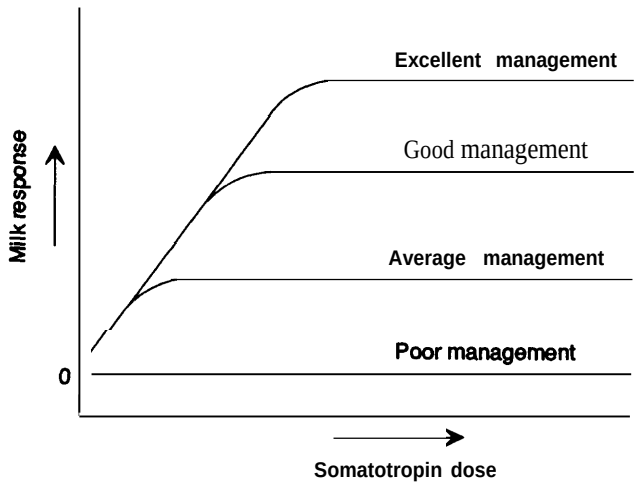
SOURCE: J L. Hennessy and N.P. **Jouppi, "Computer** Technology and Architecture: **An Evolving Interaction, "** *IEEE Computer* **September:18, 1991**

3. forecasting the behavior of a system (i. e.. simulation).

Expert Systems

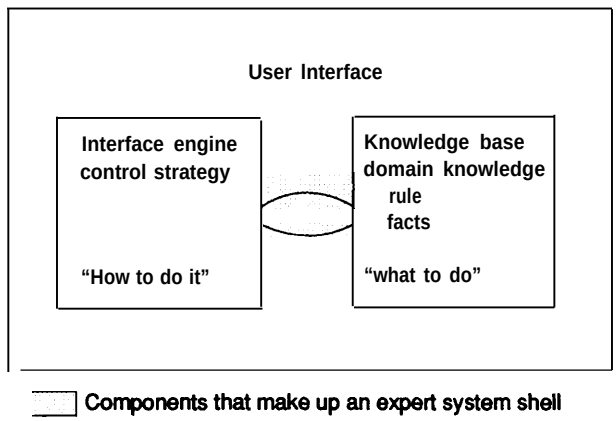
Expert systems are the most popular knowledge-based technology in agriculture. The main benefit of expert systems is that they emphasize knowledge acquisition. not programming.

Figure 4-3—Effect of Quality of Management on Milk Response of Dairy Cows Receiving bST



SOURCE: D.E. Bauman, "Bovine Somatotropin: The Cornell Experience." Proceedings of the National Invitational Workshop on Bovine Somatotropin, USDA Extension Service, Washington, DC, pp. 46–56.

Figure 4-4—Structure of an Expert System



SOURCE: Office of Technology Assessment, 1992

Expert systems are distinguished by a unique structure that separates ''What to do' from ''How to do it' (figure 4-4). The knowledge base tells the program what to do. It contains the expertise for solving the problem without the control structure found in traditional programs. The second component of an expert system is an ''inference engine' that, in effect, shows the program how to do the task at hand. The inference engine contains the control strategy that determines how to combine domain knowledge to solve the problem.

Domain knowledge can be represented in the knowledge base in several different forms, the most common

of which is rules (e. g., "If the leaves are brown, then apply insecticide X' see box 4-A). Rules correspond closely to the natural reasoning of experts, are modular, and are easy to maintain. As a result. expert systems are easy to develop and to support. The knowledge in an expert system tends to be symbolic instead of numeric. This feature allows rules to be "heuristic" in nature, akin to "rules-of-thumb. " When exact algorithms do not exist, the rules represent the expert's best guess (94).

Another interesting feature of expert systems is their capability of incorporating uncertainty into rules. For example, the rule "If the leaves are brown, then apply insecticide X; 0.3' means that there is a 30-percent certainty or confidence in the conclusion. Strategies have been developed for combining the uncertainty of rules to give a confidence value for each recommendation (7, 76). Therefore, the expert system is able to make recommendations even when the circumstances of the problem are uncertain. This ability mimics the reasoning of an expert. Expert systems have the added capability of explaining the reasoning used to derive a solution (see box 4-B), much as an expert might. The explanation is a map of the rules chained together by the inference engine (102).

Because expert systems separate the inference engine and knowledge base, it is easy to remove the knowledge from the expert system. leaving a shell that can be reused in other applications. The shell contains the inference engine, user interface. and other domain-independent modules. The first expert system shell was EMYCIN, which resulted when the knowledge base was removed from MYCIN, an expert system that diagnosed human blood diseases (89). Expert system shells have become saleable products, and several are commercially available for use in agriculture (14).

There are numerous examples of expert system applications in agriculture. These systems have tended to be diagnostic systems for addressing relatively narrow problems. Large-scale, broad-based expert systems have not been developed in agriculture. The following overview of agricultural expert systems includes systems developed for business decisions. animal production, and crop production.

Farm and Area-Wide Management—effective de-cisions regarding the planning, organization, and control of a farm enterprise are essential to agriculture. The legislative, economic, and environmental demands placed on farmers and government agencies that implement agricultural policy create a need for tools that help make sound farm-level and regional policy decisions in agriculture. Tools that help with agricultural problems at a watershed or farm will become increasingly important in the future. This will involve integration of expert systems with geographic information systems, area-wide monitoring systems (78), and remote sensing.

The financial difficulties of the 1980s vividly document the cost of poor decisionmaking in the business sector. However, a major obstacle impedes the adoption of expert systems in making business decisions. Business decisions. unlike production decisions, are generally in-

Box *4-A—An* Example ***Rule for an Expert System***

IF

- you are willing to speculate for higher prices AND
- the price trend is up **AND**
- **the basis trend is weakening** AND
- the basis trend is not expected to reverse soon AND
- the timing is **harvest AND**
- **the** type of available storage is farm OR
- the type of available storage is commercial **AND**
- you need downside price insurance **AND**
- Storage revenues are greater than storage costs, THEN
- forward contract your grain and buy **call** options.

SOURCE: R.H. Thieme et al., "Expert System Techniques Applied to Grain Marketing Analysis," *Computers and Electronics in Agriculture* **1:299, 1987.**

Box 4-B—An Example of an Explanation Provided by an Expert System

I conclude that the patient has dreaded lurgy caused by bug-eyed germs with a certainty factor of .76.

WHY:

I concluded that the patient's dreaded lurgy was caused by bug-eyed germs because tight abdomen (E3) and acid saliva (E4) indicate swelling of the spleen (E), which taken together with yellowish skin cast (D) provide evidence (CF = .76) that bug-eyed germs are the cause of the dreaded lurgy.

SOURCE: M. Van Horn, ***Understanding Expert Systems,*** Bantam Books. New York, NY, 1986.

fluenced by values, goals, and risk attitudes. Thus, two experts with the same knowledge and expertise may select different courses of actions (91).

Only a small number of expert system applications is available for farm decisionmaking. Most existing expert systems in this area relate to design, planning, and control. Unfortunately, such functions are considered relatively unimportant by farm managers. Expert systems dealing with data acquisition and interpretation, prediction, and monitoring have not been developed. This may indicate that expert system development efforts are focusing on applications not in the area of greatest need for farm managers (91),

Farm-level planning and financial analysis are active areas of expert system development. Several prototype systems are under development. One effort at farm-level planning directed at farmers' needs is the Crop Rotation Planning System (CROPS) developed at Virginia Tech (6). This system uses a map-based interface to let farmers enter data about their land (soil type, topography, landuse, and field sizes) and their farming enterprise. Based on these data, CROPS provides farm-level or field-level environmental risk evaluations for soil erosion, and nutrient and pesticide leaching and runoff. It then uses Al planning and scheduling techniques to generate a whole-farm production plan so that the overall farming operation can meet user-defined yield and/or acreage targets, economic return goals, while also reducing potential environmental risks to acceptable levels. The system runs on Apple Macintosh 11 systems and is adapted for use by the Soil Conservation Service and the Virginia Department of Conservation and Recreation in their farm planning activities.

The best known farm financial system is the Agricultural Financial Analysis Expert System (AFAES) from Texas A&M University (63). AFAES consists of a spreadsheet to prepare operating-year and multiyear financial statements; a program that calculates financial ratios and trends from the spreadsheet; and two expert systems that develop a performance operating-year analysis and multiyear analysis, respectively. This expert system operates on an IBM-compatible microcomputer and is marketed through the Texas Agricultural Experiment Station at a variety of prices based on the type of user making the purchase.

Other agricultural expert systems have been developed for specific business decisions. One example is the Grain Market program developed at Purdue University (98). This system provides advice for marketing storable commodities (e. g., crops). An example rule from this expert system is shown in Box 4-A. The machinery selection process is aided by the Farm-level intelligent Decision Support system (FINDS) (49). This system integrates a linear program (REPFARM), a database management system, and an expert system. The expert system is used to form the link between the linear program and the user and to interpret the output of the linear model. The linear program component operates on a minicomputer, but the other components operate on a microcomputer. A decision support system for planning of land use and forage supply for a dairy farm has been developed in Denmark (34). The main components of the system are a knowledge base, a linear programming model, and a PASCAL program connecting the knowledge base, model, and interface. The model integrates the varied business activities of a dairy farm, such as crop production, storing feeds, milk production, and utilization of manure. Interactions between feeding and production of milk and meat are established by use of knowledge sets. The user interface allows for consequent analysis and can function as a tool for calculation and optimization planning.

In addition to agriculture-specific expert systems for business decisions, nonfarm business systems will impact agriculture (91). For example, Dologite (24) developed the Strategic Planning Advisor to provide strategic planning advice. This system provides recommendations such as:

- Get out of a business.
- Hold current position.
- Focus on one market niche.
- Invest selectively.
- Invest aggressively.

Animal Production—Expert systems for animal production deal with the management of farm animals and generally focus on disease diagnosis and suboptimum performance identification based on technical expertise.

Most expert system activity in the area of animal production focuses on the dairy industry. There are at least two reasons for this. First, the dairy industry has a national data recording system (i. e., Dairy Herd Improvement, DHI), that provides centralized databases from which expert systems can be built (99). A second reason is that dairy animals are generally housed in confinement, and they produce a product (i.e., milk) that can be routinely monitored on an individual animal basis. This is conducive to intensive management. Spahr et al., (92) outlined several potential applications of expert systems for dairy herd management.

Some of the earliest dairy expert systems were developed by Extension Specialists at the University of Minnesota. Their first system (DMGTSCOR) ranks dairy-herd management strengths and best opportunities for improvement using DHI management measures (16). Management action is suggested for the three best opportunities for improvement. A second system, SCCXPERT, was developed to diagnose herd mastitis problems using DHI somatic cell data and to recommend corrective actions. Another system, BLKTNKCL, provides interpretation and information about bulk tank culture data for primary mastitis causing organisms. A fourth system, MLKSYS, provides expertise to troubleshoot operational and design problems with a milking system (15). Two other systems have recently been developed to assist in manure management and to provide an overall analysis of the production and financial status of a dairy farm. All of these systems were developed in the Level 5 expert system shell; as a result an effort is underway to integrate them into a single system to allow data sharing among the programs. These expert systems are distributed by the Dairy Extension office at the University of Minnesota freely to extension personnel and commercially for $75 (17).

Tomaszewski and others at Texas A&M University have developed a Dairy Herd Lactation Expert System (DHLES) to analyzes DHI milk production data and to provide recommendations for improving milk production (106). DHLES contains a separate module (LacCurv) to graphically display lactation curves. This system was developed in PROLOG and operates on an IBM–compatible computer. It is marketed through Texas Dairy Herd Improvement Association for $99 (100).

Several expert system projects are under development for the dairy industry. Kalter and coworkers (45) are developing a comprehensive expert system (Dairy Pert) to evaluate dairy-herd management. The impetus behind this effort is the possible future adoption of bovine somatotropin (bST), but the system has general applicability. This system currently contains over 320 rules in the Nexpert expert system shell, a spreadsheet-based nutrition model, and entry and advice routines based on Fox's database management software. DairyPert does not utilize DHI data because of inconsistencies among the nine national Dairy Record Processing Centers. DairyPert is funded by and will be distributed to the private sector through a large pharmaceutical company. Cornell University will distribute the system to public agencies and institutions. Oltenacu et al. (73) are developing a reproduction expert system that will analyze DHI reproductive records and determine weaknesses in the reproductive program. This system utilizes LISP on an IBM workstation. Allore and Jones (42) are developing an expert system to evaluate DHI somatic cell counts that will identify areas of management that predispose cows to mastitis. This system is being developed in CLIPS and will operate on an IBM-compatible microcomputer.

Oltjen et al. (74) have developed a prototype expert system that recommends whether to keep or cull commercial beef cows. The rules contain knowledge relating to the cow's age, body condition score, calving difficulty, structural correctness, health, and previous reproductive performance. The expert system was integrated with a simulation model to calculate net present value for each animal. This expert system was developed in the CALEX expert system shell.

An expert system to assist in the management of a sheep enterprise has been developed in Scotland (104). This system was developed without the aid of an expert system shell. Once a working prototype that could be delivered to an agricultural unit was developed, this project was halted as a research project. Expert systems for the management of sheep flocks are also under development in Australia.

CHESS is a Dutch decision-support system designed to analyze individual swine breeding herds within an economic framework (22). It determines strengths and weaknesses in the management of a pig enterprise. CHESS consists of a decision-support system and three expert systems. The decision-support system identifies and assesses the importance of relevant deviations between performance and standards. The expert systems combine and evaluate deviations to identify management strengths and weaknesses.

XLAYER (84) is a management expert system for the poultry industry and is one of the most comprehensive expert systems in animal production. XLAYER is designed to diagnose and estimate economic and associated losses as well as recommend remedial management actions for over 80 individual production management problems significantly affecting a flock's profitability. An example output is shown in box 4-C. This system contains over 400 production rules and was developed in the M1 expert system shell.

Crop Production—All commercial crop production systems are potential candidates for expert system applications. In particular, expert systems should be considered for integrated crop management decisions that would encompass irrigation, nutrition, fertilization, weed

Box 4-C—An Example Recommendation From XLAYER

You are **experiencing an economic loss of about $725** per week because of a sudden change in the grain portion of your layer ration. Reformulate the ration and phase in new grains gradually, even if the cost per pound is higher.

Production losses amounting to some $500 per week are being experienced because temperature in your layer house is exceeding 29.4 degrees Celsius. Use artificial cooling systems in regions where hot weather is expected to continue. If layer barn has no cooling system, construct a partial budget to evaluate alternative pooling systems such as evaporative cooling pads, roof sprinklers, high pressure misting and other forms of cooling,

Water intake is very low. Check watering systems to make sure that birds are getting adequate fresh, clean water.

Equipment repair costs are running $100 per week higher than normal. Check management practices related to the routine servicing of mechanical equipment. If repair and maintenance costs are consistently high, construct a partial budget to evaluate the replacement of old or poor functioning equipment.

SOURCE: E. Schmisseur and J. Pankratz, "XLAYER: An Expert **System for Layer Management," *Poultry Science* 88:1047, 1989.**

control-cultivation, herbicide application, insect control, and insecticide and/or nematicide application (64).

The first expert systems developed in agriculture were PLANT/ds (65), a program developed at the University of Illinois that identified diseases of soybeans in Illinois. and POMME(81), developed at Virginia Tech to identify diseases of apple orchards. Both were written by computer scientists who were using agriculture as a novel domain. Michalski, for example, was primarily interested in machine learning.

Of the major crops, cotton has received the most attention to date, with at least three expert systems and one simulation-based management model now available to the public (94). COMAX (COtton MAnagement eXpert), the expert system component of GOSSYM/COMAX was developed by the U.S. Department of Agriculture, Agricultural Research Service (USDA/ARS) in Mississippi (56).[1] Users of this system purchase a weather station linked to a personal computer running the program. The GOSSYM component is a simulation model of cotton production that uses weather data collected from the weather station. The COMAX expert system uses the model to project when to irrigate and fertilize to achieve optimal agronomic goals. The entire GOSSYM/COMAX system including the weather station and computer costs several thousand dollars. Despite the high price tag, it is used by as many as 500 cotton farms in 15 States.

COTFLEX is an integrated expert system and database package developed at Texas A&M and released to the public through the Cooperative Extension Service (93).

Photo credit: U.S. Department of Agriculture, Agricultural Research Service,

Farmer and consultant examine data from COMAX (Cotton MAnagement eXpert) computer program.

The overall system will eventually include a whole-farm economic analysis module that lets farmers evaluate whether or not to participate in Federal farm programs or to purchase Federal crop insurance. The component released to the public, however, is devoted to insect pest management of the three major insect pests of cotton in Texas.

CALEX/Cotton is another integrated cotton expert system and database management tool (79). CALEX was developed as an expert system shell, and cotton was the

[1] GOSSYM is a hybrid term formed by combining *Gossypium*, the scientific name for cotton and the word simulation.

Photo credit U.S. Depatment of Agriculture, Agricultural Research Service.

Farmer and engineer check automated weather station that feeds daily weather information into the COMAX system to update its prediction for cotton yield and harvest dates.

first application area. The system was supported through California's statewide integrated pest management program and delivered to farmers for testing and use. It is one of the best-documented attempts at delivering expert systems to farmers for use in crop production (31). Because the program was developed with State support, no revenue has been collected from its users and the project continues to depend on State support.

Pennsylvania State University supports a laboratory devoted to the development of expert systems and their delivery through the Cooperative Extension Service. The University has developed several expert systems using an expert system shell (PENN-Shell) developed in-house. One of these expert systems, GRAPES, recommends pest control options for insects and diseases in vineyards (83). Penn State's expert systems all run on Apple Macintosh computers, and the University supports a statewide computer network for these machines.

USDA-ARS researchers (28) developed a knowledge-based system for management of insect pests in stored wheat. The system determines whether insects will become a problem and helps select the most appropriate prophylactic or remedial actions. Simulation models of all five major insect pests in wheat have been developed; the model's output feeds the expert system.

Evans and coworkers (26) at the University of Manitoba have developed an expert system to serve as a Fertilization Selection Adviser. The current system considers only one type of crop (wheat), four different moisture regimes (arid, dry, moist, and irrigation), one soil nutrient (nitrogen), and four different fertilizer compounds (urea, ammonium nitrate, urea ammonium nitrate, and ammonia). It provides return on investment information; a risk analysis module is under development. This system was developed in the LISP programming language for the Macintosh: however, work has already begun to develop a similar system using the C programming language cm an IBM-compatible microcomputer.

In general, one can find expert system applications for crop production for virtually all the major crops in this country and in many countries around the world. Insect pest management, weed control, and disease identification are the most common domains. Other systems that have received wide recognition in crop systems include:

- EasyMacs, an expert system and database program developed at Cornell University for recommending pest management strategies for apple production;
- SOYBUG, an expert system developed in Florida that helps farmers with insect pest control in soybeans (2);
- SIRATAC, an expert system and simulation model developed in Australia for helping cotton farmers with pest management decisions that has since been marketed internationally (36);
- TOM, an expert system for diagnosing tomato diseases developed in France (5); and
- WHAM, a wheat modeling expert system developed at the University of Melbourne, Australia (3).

Research Needs— Development of commercial expert system shells is being driven by forces outside agriculture

and is proceeding at a relatively rapid rate. However, agriculture applications generally will require expert system shells to operate in a microcomputer environment whereas industrial applications often reside on workstations or minicomputers. Since this is a domain-independent problem, it may be best addressed by computer scientists outside of the agricultural sector.

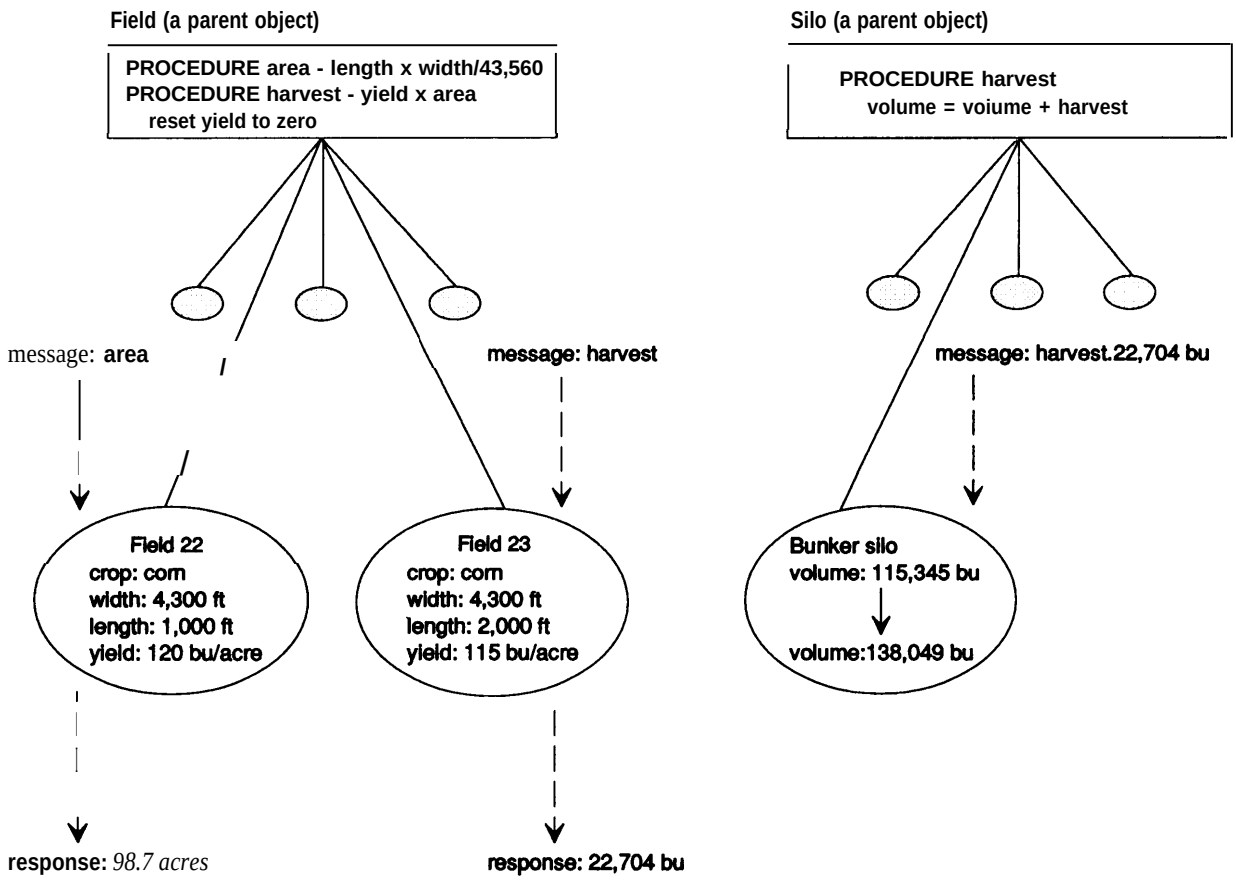
The main limitation to development of expert systems is adoption of computer technology. To promote this area will require more trained personnel and incentives to develop and deliver computer systems.

Object-Oriented Simulation Systems

In addition to expert systems, another type of knowledge-based system that is useful for planning is object–oriented simulation. Traditional simulation systems model the *behavior* of a system by explicitly simulating individual processes. The ***structure*** of the real system usually is implicit in the model. Object-oriented simulation models have an inverse structure; they explicitly model the *structure* of the real system, and the *behavior* of the system is implicit in that structure.

Each component of the real-world system is represented in the simulation as an object. Objects are units that consist of self-descriptive data and procedures for manipulating that data. Objects can be represented in a hierarchy such that they inherit properties from more general categories (i.e., their parents). For example, an object-oriented simulation of a farm (figure 4-5) would contain a general FIELD parent object that describes the general features of all fields (e.g., a method to calculate the area of the field). Individual fields (e.g., field 23) would be represented as unit objects that inherit the properties of the parent FIELD object and may also contain some information specific to themselves (e. g., current crop planted in the field). Objects in object-oriented systems communicate by exchanging messages. For example, if field 23 is to be harvested, a HARVEST message is sent to the field 23 object. The field 23 object handles the details (internally resetting its own values) and returns the amount of crop harvested. This return message can

Figure 4-5—System Structure for an Object-Oriented Simulation System



SOURCE: Office of Technology Assessment, 1992.

be sent to a particular silo object which knows how to add the crop to its inventory. Once the object-oriented system is developed, the simulation sends messages to appropriate objects in a fashion similar to farm managers giving orders to their employees.

There are two main advantages to this type of simulation. First, the model closely corresponds in structure to a real system. This facilitates maintaining and expanding the model. Second. procedures in an object can be represented in a symbolic fashion similar to expert systems. Thus, object–oriented simulation can be used to model processes that may not be quantitatively well defined.

Object-oriented simulations have been under development since the early 1980s. An early object-oriented simulation language (ROSS) was developed in the LISP programming language by the Rand Corp. for the Air Force (62). This language has been used in military applications. Two early examples are SWIRL, an object-oriented air battle simulator, (47) and TWIRL, an object-oriented simulation for modeling ground combat between two opposing tactical forces (48).

Object-oriented simulations are powerful tools for modeling the behavior of biological systems that are otherwise difficult to describe mathematically. Output from these systems can be used in planning and to determine impacts of changing management procedures. However, most existing object-oriented simulation models cannot easily be transferred to production agriculture.

Several object-oriented simulation projects have been developed specifically for agriculture. Researchers at Texas A&M University developed an object-oriented model to simulate animal/habitat interactions (82). The simulation was specifically used to study the damage caused by moose migrating through forest plantations. This system was developed on a Symbolics workstation using LISP. Another agricultural simulation was developed by USDA-ARS to model insect disease dynamics in a rangeland ecosystem (9). This model is primarily a research tool for studying the relationship between grasshoppers and their pathogens to assist in integrated pest management programs. This system was also developed on a Symbolics workstation using the FLAVORS object–oriented programming language. Another LISP-based system was the host-parasite model developed by Makela et al. (58) to study the interaction between the tobacco budworm and one of its parasites in cotton fields. More recently, Crosby and Clapham (18) used the Smalltalk language to simulate nitrogen dynamics in plants; Stone (95) used an object-oriented model of a mite predator-prey system to show that chaotic dynamics rather than stable or predictable cycles, might be the norm in agricultural systems; and Sequeira et al. (87) developed an object-oriented cotton plant model for use in studying the interaction between localized pest feeding and cotton lint yield and quality. Another object-oriented simulation project is under development by Chang and Jones at Cornell University for use in agriculture (10). This project uses a LISP-based, object-oriented programming language (B-object, Kessler, University of Utah) to model the operation of a milking parlor. When completed, this model will be useful to dairy–farm managers and their consultants for parlor configurations and for identifying changes in performance when changes in parlor operation are made.

Research Needs—The general paradigm of object-oriented programming is being incorporated into several traditional programming languages (e. g., C, PASCAL), but few inexpensive commercial shells exist in which to develop object-oriented simulations. Smalltalk is a good example. It is a language and a development environment in one, and it generally comes complete with many predefine object classes developed specifically for simulation. Other expert system shells like KEE, Goldworks, NExpert-Object, and Level-V Object include the object-oriented paradigm and can be used for simulation. LISP offers many advantages for prototype systems such as the parlor project. However, LISP is not a language in which final products should be delivered, since it requires too much memory and is too slow for agricultural applications. More research is needed to determine the potential value of object-oriented simulation for agriculture.

Knowledge-Acquisition

Knowledge-based systems are powerful computer tools because they contain and apply a significant amount of expert knowledge to problem-solving; however, this also constrains systems development. Knowledge acquisition is a slow and tedious process, and problem-solving rules and procedures are often hard to articulate.

Artificial intelligence can help automate one type of knowledge acquisition (21, 66), that of rule formation. Machine learning, for example, is an artificial intelligence technique for automatically generating rules from a set of examples. This is sometimes called “learning from examples. ” It can be used to assist experts to develop rules or fill in where experts do not exist. For instance, rules for a crop disease diagnostic expert system can be generated using a machine learning system with a database of plant descriptions and associated diseases.

Michalski and others (65) compared rules derived by experts and those generated by a machine learning algorithm (AQ11) when developing an expert system for soybean disease diagnosis (PLANT/ds). The database consisted of 630 examples based on 35 plant and environmental descriptors for 15 soybean diseases. One rule was generated for each disease. When tested in an expert system, the machine-generated rules outperformed those generated by experts. The machine rules properly diagnosed 98 percent of the test cases while the expert derived rules diagnosed 72 percent correctly.

A microcomputer-based machine learning system has been developed for agricultural problems (27). This system was first used to generate rules for a grass identification system (WEEDER). Other generic machine-learning algorithms are available as commercial products (e. g., *Classification and Regression Trees,* California Statistical Software, Inc, Lafayette, CA; ID3, Knowledge Garden, Naussau, NY).

Due to the nature of rules generated from machine learning (i.e., the rules indicate which variables are important for describing certain results), machine learning can also be used as a data analysis tool. Liepins et al. (57) investigated the use of three machine learning algorithms for analyzing natural resource data. They studied the effect of storm damage on lake acidification using a data set generated after a major storm stuck the Adirondack Park in upstate New York. Application of machine learning to these data provided no new information but reinforced many of the discoveries made using traditional statistics. Dill (23) also used a machine-learning algorithm to analyze the sale price of cattle sold at public auction. The data set contained all information available to a buyer on sale day and the price for which the animal was sold. Using machine learning. Dill was able to determine which variables influence the buyer's decision and now will be able to generate an automated appraisal system from these results.

Research Needs—There are several problems associated with machine learning. One concerns data that contain random errors (i. e., ''noisy' data). Some machine-learning algorithms are unable to handle this type of data while others perform poorly **(57).** Much of the data in agriculture is noisy. Another problem is that many of the machine-learning algorithms require discrete data (e.g., classification-based) while agricultural data is mainly continuous (e. g.. numeric). A third problem is that machine learning requires a complete database with associated outcomes from which to operate. Few of these databases exist in agriculture.

Despite these limitations, machine learning can be a very valuable knowledge acquisition tool in certain situations. With continued development, these limitations will likely be overcome.

Knowledge-Based Report Generation

One of the initial goals in artificial intelligence was to develop systems capable of translating documents from one computer language to another (I I). An integral component of machine translation is developing a knowledge representation of the original document such that text can be generated in another language. Though machine translation will not have a major impact on American agriculture, systems that are able to generate knowledge-based reports from a database will.

Farmers receive large volumes of production data with little or no interpretation; hence, they may be unable to convert these data into useful information. Knowledge-based report generation is an emerging technology that can provide them with interpretive reports to better support management decisions.

In many respects, programs for knowledge-based report generation are similar to expert systems. Report generation programs contain four components:

1. a domain-independent knowledge base of linguistic and grammar rules,
2. a domain database from which the report is to be generated,
3. a domain knowledge base for interpreting the data structure, and
4. the text planning component for deciding what to say and how to say it (69).

Once a system is complete, the domain knowledge can be removed to create a shell that can be used in another domain. Report generation is still largely in the research stages and commercial shells have not been made available.

CoGenTex, Inc. has developed a proprietary linguistic shell for knowledge-based report generation. This shell has been used to generate weather forecasts in both English and French for the Canadian Government. A USDA Small Business Innovation Research proposal has been submitted to study the suitability of this approach for generating knowledge-based reports that interpret DHIA records for dairy farmers (46).

Research Needs— To date, there have been no applications of knowledge-based report generation in agriculture. Research should be directed at investigating the potential benefit of this technology to American agriculture. Once the preliminary investigations are com-

pleted, a better understanding of needs and benefits will be established.

Interfacing Technologies

Farmers have been slow to adopt personal computers. Recent surveys indicate that only 15 to 27 percent of farm managers utilize computers in management (1, **55).** Two factors that may have contributed to this slow adoption rate are the lack of high quality management software (71) and a computer phobia on the part of some farm managers. Farm managers have available to them only a limited selection of computer programs. most of which perform similar functions. The computer phobia is caused by a lack of exposure to computers but is exacerbated by the type of user interfaces (both hardware and software) employed by most agricultural computer programs.

Hardware Issues

Currently, most microcomputer systems use a keyboard as the major input device. Keyboard entry is clumsy for agricultural software as many farm managers are slow typists. Even for programs that require little input. a ‘ ‘hunt and peck’ typing ability can frustrate the user to the point of not using the system. Another problem with keyboard entry is impaired dexterity from excessive physical labor or injury that severely impairs the farm manager’s ability to type. Consequently, software should be developed allowing the use of alternative input devices.

Two relatively common input devices are the mouse and the light pen. However, neither of these capture the user’s natural pointing instincts **(77).** A more intuitive input device is the touch-sensitive screen. Another alternative input device is speech.

Touch-sensitive screens are computer displays in which portions of the display may be used as an input device. This technology has been available since the mid-1960s (41). Touch-sensitive screens are easy to learn, very durable, and require no additional work space. At the same time they have the disadvantage of increased cost, increased development complexity, lack of software to take advantage of touch-sensitive screens, arm fatigue. and screen smudging. A major complaint of touch-sensitive screen users is the lack of precision; however. high-precision screens have recently been developed (86). Due to their durability and user-friendliness, touch-sensitive screens have been used in specialized applications such as kiosk information systems in shopping malls and airports and for order processing in restaurants. Both of these applications have been developed to allow control of a computer systems by nontechnical users.

A second area of research aimed at improving the physical link between the computer and user is speech recognition. This research has been glamorized by science fiction movies such as 200 l: A Space Odyssey, in which computers carry on a dialogue with the user. Though this is the goal of research efforts, it is not the current state-of-the-art (52). A prominent researcher has predicted that totally spontaneous, unrestricted speech recognition is still as much as 30 years from fruition (105). However, speech recognition appears to be suitable for applications with restricted discourses. Agriculture is one such application.

Speech recognition is based on the ability to distinguish between words and on natural-language processing whereby natural language input is transformed into a form that the computer can utilize. In a common method for speech recognition, template matching, each spoken word is matched against a predetermined lexicon. The lexicon must be trained to recognize a user’s voice. thereby resulting in a user-specific system (52). High-performance, speaker-independent, continuous-speech recognition systems use another approach. that of statistical modeling. Commercial speech recognition systems range from speaker-dependent, single-word recognition (64-word vocabulary units) to speaker-independent, continuous-word recognition (40.000-word vocabulary units) (75).

Speech recognition is not a perfect function. Most literature values for recognition accuracy range from 95 to 99 percent (97); some articles report 8 to 12 percent error rates (61). Several factors affect the error rate; these include presence of background noise. phonetic similarity of words, and mood of the user as he/she alters voice quality (52). Furthermore, lack of a one-to-one correspondence of sounds to words distinguishes speech from other inputs. For instance, when a key is pressed on the keyboard, the output is unambiguous. With speech recognition, the output is the *most likely* output which corresponds to the input. Consequently, the performance of current systems degrades (in both time and accuracy) as the vocabulary increases. When speech input was compared to traditional input methods, it was found to require the same amount of time as mouse input, 80 percent as much time as a single key stroke and 48 percent as much time as full-word typed commands (61).

A commercial speech recognition system recently was added to a medical diagnostic system for clinical data entry (88). The system was an isolated-word, speaker-dependent system capable of recognizing eight continuous syllables. Utterances required a half a second to

take effect and 90 percent of all utterances were recognized correctly. For this application, speech recognition proved an effective interface for improving the acceptance of the diagnostic system.

Advances in hardware input devices to improve the usability of computers are being driven by multiple nonagricultural sources. For example, speech recognition is a goal of the Department of Defense (105) and of research aimed at providing more environmental control to the physically disabled (20). Since this technology is domain independent, advances in other domains should also greatly facilitate the use of speech recognition in agriculture during the next decade.

Software Issues

The software design of the user interface is the main factor determining the effort required both to learn and to use a computer program. The most important function of the user interface is to match the needs of the user. Novice users need interfaces that are easy to learn while advanced users prefer interfaces that are easy to use. Most easy to learn systems are not convenient to use. Thus, no one interface will meet the needs of all computer users (33).

In general, agricultural software has not been distinguished by sophisticated user interface designs. This partly reflects the fact that most agricultural software is written by people who understand agriculture. yet have little or no training in user interface design.

Currently. there are nearly a dozen different interface designs that can be used with computer programs. These range from command languages to natural language.

Two common user interface designs in agriculture are command and question/answer systems. A command-driven user interface is similar to the DOS system where a series of commands and arguments have to be known by the user. For example. in the Cornell Remote Management System, which is used to ascess DHI data. a command such as **AIM 1-S1-DH1MO094 is** used to run a report. This type of user interstice is easy for an expert to use, but because it is not intuitive. it is difficult to learn. Another type of command-driven user interface can be designed by mapping commands to special keys. This interface is used by WordPerfect (WordPerfect Corp.. Orem. UT) which uses multiple combinations of the SHIFT. ALT. and CTRL keys with function keys forspecific commands. Question/answer systems require the **user to enter a response. If the type of response is** unambiguous, this design can be easy to use but also tedious. This type of user interface should be limited to responses which are Yes-No (e. g.. Y/N) or numeric.

A type of computer interface that is more intuitive to use than command and question/answer systems is natural language. With this type of interface, commands are given in normal spoken or written language instead of a formal command language. An example of a natural–language user interface is one that converts natural-language commands to DOS commands. For example, the natural-language command ‘‘show me the files on drive b:” is converted to the command “dir b:*.*” (53). Another example of a natural-language interface is one that was developed for signal processing (68). This system allows users who are knowledgeable about signal processing but ignorant of any programming languages to manipulate wave forms using English commands oriented toward mathematical operations. However. the most common use of natural-language interface has been in database querying systems.

Natural language is attractive to the casual user and to the user who is unwilling to learn a formal command structure. However, natural-language user interfaces require more typing than command-language interfaces. As discussed previously, typing requirements are an important consideration for agricultural software. Therefore, natural-language is probably not a desirable user interface for systems that can be driven with a limited set of commands (e. g.. DOS).

Another popular user interface design is the menu system. In the simplest form. a menu is a list of choices. The user selects one choice by entering a number or letter. Another version includes a light bar that can be positioned over the menu using the keyboard. A more sophisticated menu design, known as the graphic user interface (GUI), is the icon and mouse system. This type of system represents menu selections **using a picture** that is ‘"clicked-on’ with a mouse. The icon system was first developed for the Xerox ‘Star’ workstation (90) to reduce the learning time of the user interface. The user is expected immediately to know which icon is appropriate. Thus. the icon must be unambiguous and realistic. Distinguishable and meaningful icons may be difficult to develop for several similar items (96). Accompanying text is often added to clarify the meaning of possibly ambiguous icons.

Another major factor of the user interface is data entry. For this factor. interfaces called “form-filling” designs have been developed. The user is presented with a series of fields in which data are entered. The display relates to a written form and allows the user to see all of the fields together. Often. form-filling interfaces have data

validation and editing capabilities. For more complex data entry needs, multiple forms arranged as overlaid windows can be used. As data are entered into a field, it actuates the next form which displays with the appropriate related fields. This type of user interface is rapid, easy to use, and easy to learn (96).

Design of sophisticated user interfaces has advanced to a point where they should now be considered for all agricultural software. Proper attention to user interface design issues can result in agricultural software that is more acceptable to use. For example, adaptive interfaces are aimed at satisfying the differing needs of both novice users and experienced users. An adaptive user interface determines the skills of the user and changes the interface to meet those skills. In general, novice users are provided with menus and question-answer systems, while advanced users are given the option to use command languages and special key strokes. A prototype adaptive interface has recently been developed (SAUCI); (101) for processing UNIX commands. Using the adaptive interface, users made about half as many errors and required less time to perform tasks. Research in adaptive interfaces should result in systems that are more intuitive to use and easier to learn.

Information Retrieval Systems

Information retrieval systems are a set of advanced computer technologies for accessing stored information. These technologies differ from decision support systems in that they offer no recommendations. Three technologies are emerging that may have a role in American agriculture in the next decade. These are natural-language interfaces, full-text retrieval systems, and hypertext systems.

Natural-Language Inter-aces—Maintaining a complete set of production records is a critical component of farm management. More important is the ability to rapidly and flexibly access information for management decisions. The best method of accessing production records has been through database management systems; however, these systems generally have inflexible retrieval facilities based on menus that present options of data to retrieve or predefine reports to run. Traditional systems require the user to learn the hierarchical structure of the menu system and limit the type of reports available. A natural-language interface for querying a database can offer a more flexible retrieval system (43).

The current generation of natural-language interfaces was made possible by a set of linguistic theories developed by Chomsky (12). These theories were first implemented in an efficient algorithm in a natural-language interface for retrieving information about lunar rock brought back from the Apollo space missions (LUNAR) (107).

LUNAR is based on a three-compartment model of data retrieval. The first compartment is syntax analysis, which determines the grammatical structure of the sentence. The second compartment of LUNAR is the semantic module, which is responsible for determining the meaning of the syntactic structures. The meaning is translated to a formal query language in this module. The third module of LUNAR is the retrieval component. This module executes the formal query language, based on the semantic analysis, to retrieve data from the appropriate database. When LUNAR was tested, it answered 78 percent of the questions presented to it (107).

The purpose of developing LUNAR was to assist scientists in retrieving data on lunar rocks. Its users were primarily interested in specific data as that data related to other scientific information that had been collected. However, this style of data retrieval is not appropriate for production agriculture where management decisions need to be made. A natural-language interface for retrieval of data for decisionmaking should put the data in the proper context so that an informed decision can be made. Consequently, a knowledge-based, natural-language interface was developed to formulate more complete, intelligent answers to users' questions from an agricultural database (IDEA) (44).

IDEA is based on the LUNAR three-compartment model but utilizes a new approach for semantic representation. Unlike the formal query language used in LUNAR, IDEA represents the query through a set of domain concepts, which contain ''expert' information. IDEA has the capability of responding to a query and offering additional pertinent information. An example of a query and answer is shown in box 4-D.

IDEA was developed for a dairy database to assist farm managers in decisionmaking. It is capable of responding to several different types of queries. The simplest query is about a single cow (e.g., "When is 5000 due to calve'?" or, simply, "Is 5000 pregnant'?"). More complicated questions can be asked about subgroups of cows (e.g., "Which daughters of Thor are bred to Bell'?"): averages (e. g., "What is the average calving interval for cows in the north barn'?'); and counts (e. g., ''How many heifers are due to calve in June'?"). Replies are designed to contain important information that the user may not have known was in the database or may not have even asked for.

Just as generic, domain-independent shells have given expert systems widespread use; for natural-language interfaces to be successfully used in agriculture, a generic natural-language shell capable of being transported to other databases is needed. However, unlike expert systems, development of a generic shell for natural-language interfaces has proven difficult. Hendrix and Walter (37) point out that full synchronization is needed between the database management system and the natural-language interface. This is difficult to achieve when the natural-language interface is added as an afterthought. For example, in the dairy database that IDEA accesses, the reproductive status of a cow is given as a numeric value (e. g., O means ''not bred' '). To access multiple databases, the natural-language interface must be able to translate all their representations.

TEAM is a natural-language interface developed at SRI and designed to be transportable between databases (32). However, a database expert still is needed to adapt the system to each new database. The expert supplies information describing the database and domain-specific words, a process that TEAM has automated through a **series of questions. Another** source of difficulty in making a natural-language interface transportable is associating meaning to phrases. For example, consider the phrases "bred to Bell" and "bred in May. " The first refers to the ''service sire' while the second refers to the "breeding date. " Most natural-language interfaces cannot handle these kinds of subtleties. Thus, for a natural-language interface to be successfully transported to a new database, a database expert and a linguistic expert are needed (19).

Because of the problems in developing generic shells, natural language commercially lags behind many other artificial intelligence technologies (70). One of the few generic natural-language interfaces available commercially is the "Intelligent Assistant" interface for Q&A (Symantic Corp., Cupertino. CA), which was introduced in 1985. This system differs from most transportable natural-language interfaces in that it has its own database system. Users build their application directly in Q&A. This system also uses synonyms for acquiring new words.

Box 4-D—An Example Query and Answer to a Natural-Language Interface

>> which cows are due to calve next week?

4897 was bred to STARMAN on 12/15/1987
and is due to calve on 09/18/1988
Projected calving interval: 347 days

>> when did 5281 calve?

5281 calved on 05/26/1988 with a heifer calf - #5535
The calf **was in good condition**
Gestation length = 278 days
5281 had a retained placenta

>> is 5239 pregnant?

YES
5239 was bred to TOPBRASS on 03/20/1988
and is due to calve on 12/19/1988
Projected calving interval: 466 days

>> **is** 5449 pregnant?

NO
5449 calved on 12/1 1/1987 with a heifer calf - #5478
The calf was in good condition
Gestation length = 283 days
5449 is 282 days in milk
5449 was bred to LEVI on 02/21/1988
5449 was pregnancy checked on 03/30/1988 and was open

SOURCE: L.R. Jones and S.L. Spahr, "IDEA: Intelligent Data Retrieval in English for Agriculture," *A/ Applications* ***in*** *Natural Resource* ***Management*** 5(1)56, 1991.

An attractive feature of this system for agriculture is that it operates on standard IBM-compatible microcomputers. Another commercial natural-language interface is Natural Language (Natural Language, Inc., Berkeley, CA). This system interfaces with any database that supports Structured Query Language (i.e.. SQL).

Full-Text Retrieval Systems—A relatively new area of human-computer interfaces that holds great promise in making information more accessible is full-text retrieval. The goal of a full-text retrieval system is to search a collection of documents to find relevant information for the user (4). These systems can be particularly useful for accessing a collection of documents that are authored by several different people who potentially use different words to express the same thing. Such a collection of documents, including most Agricultural Extension publications, is unedited and generally not indexed.

Blair and Maron (4) evaluated the effectiveness of STAIRS (STorage And Information Retrieval System). a full-text retrieval system developed by IBM. They found it to retrieve less than 20 percent of documents relevant to a particular search when the database contained roughly 350,000 pages of text. They identified several pitfalls that need to be considered in developing full-text retrieval systems. STAIRS was efficient at retrieving documents that exactly matched the wording of the request, but it performed poorly in retrieving documents that contained misspelled words, and words that were synonymous with those in the request. For example, the word ''gauge' was spelled [9]'guage' in an original document, preventing its retrieval. Full-text retrieval systems must be able to account for such situations and retrieve relevant documents whose text may not match the exact wording of the request. A simple key-word search or an indexing scheme thus does not meet the needs for full-text retrieval.

A full-text retrieval system developed by Gauch and Smith (30) contains an expert system and a thesaurus. The thesaurus contains domain-specific information for words, a list of synonyms for each word. its parent word(s), and a list of children words. This structure allows a particular search to be generalized or narrowed. Decisions as to the search pattern are made by the expert system. If the recall is low, it will broaden the search. If the precision is low (i.e., too many irrelevant passages are retrieved) the expert system will use a more specific search. The query is formed by the user and then passed to a full-text retrieval system that has immediate access to any passage in the text. The retrieval system requires that the text undergo two stages of preprocessing. In the first stage, the text is formatted for enhanced display. Formatting includes insertion of format marks (line. tab. italics, line, label) and context information (section. paragraph, sentence. item). In the second stage of preprocessing. the file is converted to fixed-length records totfast access. Consequently. the system does not operate on the original documents. This is an undesirable feature as it precludes searching subsets of documents and requires additional storage.

A full-text retrieval system now commercially available (Metamorph; Thunderstone, Chesterland. OH) should have wide application in agriculture. Metamorph operates on standard ASCII files using natural-language queries to search and find relevant passages in documents. The natural-language input undergoes morphological analysis to normalize each word. The normalization process converts words to morphemes—the smallest meaningful unit of a word. A set of morphemes that are related to, but not necessarily synonymous with. the original morpheme is generated. Metamorph then correlates these equivalence sets to textual passages to determine passages that relate to the natural-language query. At the first level of search, an equivalence must be present in the passage for its retrieval. If this is unsuccessful, Metamorph will broaden the search. Another important feature of the correlation procedure is that it utilizes an approximate match to account for minor discrepancies in spelling. These features fulfill the conditions Blair and Maron (4) identified as necessary for a full-text retrieval system.

Numerous applications of full-text retrieval are possible. A recent project used a commercial full-text retrieval system to assist users in querying a specific DHI computer manual (29). Additionally, with the advent of mass storage systems for microcomputers (e. g., CD-ROM), full-text retrieval systems can play a significant role in providing expert information (e. g., extension bulletins) to county extension offices and directly to farm managers. An effort is underway to develop a national dairy database (39) consisting of full-text documents covering major dairy-management areas. This full-text database is expected to be delivered ***on*** a CD-ROM and accessed using a full-text retrieval system.

Hypertext-Hypertext is a method of connecting related passages of text, graphics, animation, or computer programs in a multidimensional {i. e., hypercube) fashion such that they can be accessed in a nonlinear fashion. Each node can be connected to any number of other nodes that provide additional related information. Hypertext systems are analogous to footnotes or references in a

document. For example, a footnote contains additional information related to the text. The reader determines when or if the footnote is to be read. Computerized hypertext systems are based on the same principle.

Hypertext systems are relatively easy to implement but are difficult to build. They require the locations of the related text to be stored with the location of the original text. This is essentially a database management problem. The difficult part of a hypertext system is to establish the appropriate links between and among nodes. This usually requires a domain expert, but the process can be automated through full-text retrieval tools.

As Extension documents begin to be disseminated in electronic form, hypertext should be considered as a method of increasing access to related subject matter. For example, an extension bulletin that describes the use of lactation curves for herd management should be linked to other bulletins describing the use of butterfat and protein curves. To demonstrate the benefits of hypertext in an agricultural setting, Rauscher and Johnson (80) delivered the six feature papers contained in an issue of *Al Applications: Natural Resources, Agriculture, and Environmental Sciences* in hypertext form.

Integrated Systems

Management of an agricultural enterprise requires a variety of decisions and, hence, a variety of decision-support tools. Long-range research in the area of human-computer interface will be directed at integrating various decision–support programs into a single system. Current research is aimed at integrating autonomous systems, developing intelligent user-interface managers, and integrating systems through a common representation shared by an intelligent dialogue manager.

An overall controlling software system that allows the user to access different decision-support tools yet maintains operational independence of tools themselves represents the lowest level of systems integration. The genera operating system of a computer is an example in that it allows the user to access multiple programs in the same environment. More advanced integrated systems assist the user in choosing the decision-support tool and provide logical links between tools. This type of integration can also be used to develop multimedia applications such as full-color, full-screen graphics; full-color, full-screen video; aural delivery of speech or music; and animation (50).

An example of an advanced multimedia system for integrating several different decision-support tools is the Whole Earth Decision Support System (WEDS; reference (51. The WEDS project combines textual databases, expert systems, simulation models, traditional programs and laser-video images within the agricultural domain into a single integrated system. Each module is developed independently and inserted into WEDS. For example, an expert system for lactation curve analysis developed independently from WEDS can be incorporated and linked with other components dealing with lactation curves (e. g., documents in the textual database). In this system, the user moves between the different modules guided by logical connections. Systems such as WEDS should be able to provide a complete information resource to extension agents, agri-service personnel, and farm managers for solving problems and formulating management decisions. The multimedia approach utilized in the WEDS project should be encouraged for systems developed in the 1990s since people remember more if they combine seeing, hearing, and doing during the learning process (60).

A more tightly coupled method of integrating software is to link different systems through a user-interface manager. The user-interface manager controls all user-interface functions for a set of application software (96) and validates all inputs for the application software. Screen displays, including error messages and on-line help, are also controlled by the user-interface manager. There are two major advantages to integrating software in this fashion. First, a system does not need to be redeveloped for each piece of application software. Second, the user is always presented with a consistent interface; thus, as the user moves from one application to another, the user interface remains the same. This is important for acceptability of software by laymen. Development of a generic user-interface manager awaits further research; however, several fourth-generation languages include facilities that can assist in development of generic user interfaces (%).

A more advanced method of integrating software is through an intelligent user interface; such an interface allows problems to be formulated and appropriate application software selected using natural language. A prototype system for integrating crop production decision-support systems is under development (see figure 4-6); (59). It uses an intelligent dialogue manager (IDM) with unrestricted natural-language communication to develop a problem description. The IDM parses input into a semantic representation using knowledge of the types of queries that can be asked and the lexical entities that can be discussed. The IDM also utilizes a model for inferring the goal of the user's input and relating it to the context of the overall dialogue. The semantic representation is passed from the IDM to an expertise module dispatcher

(EMD), which selects the application to respond to the query and formulates the appropriate control structure for the application software. The EMD is an expert system with knowledge of the problem-solving abilities of each application software module. This system can provide the user with a variety of problem-solving tools. Furthermore, the user does not need to know the nature of the software, the details for using it, or the situations for which it is appropriate.

Other Computer Technologies

Three other emerging computer-oriented technologies will impact American agriculture in the 1990s. The first involves dispersal of information to those who need it in different geographic localities. The second. robotics, will impact the labor problems associated with agriculture. The third area is sensor technology.

Networks and Telecommunications

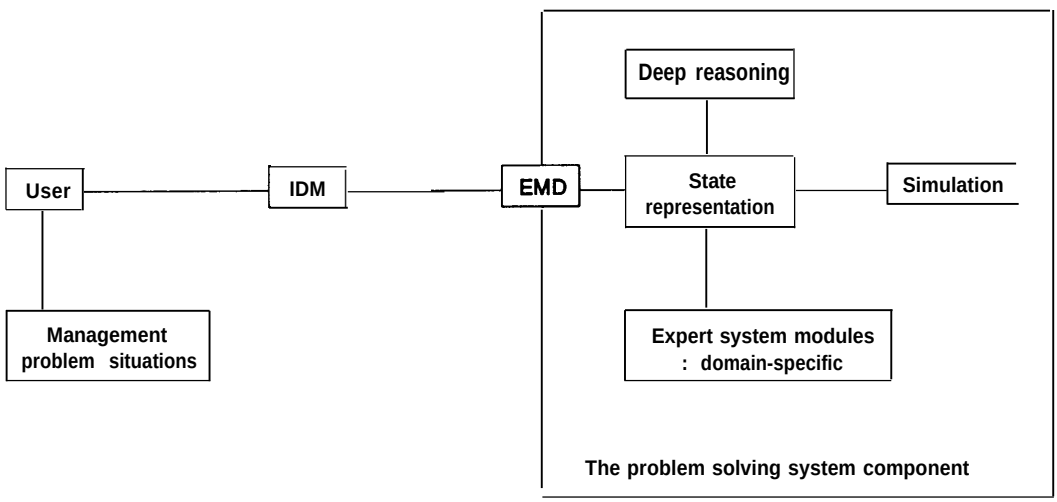
American agriculture is decentralized and widely distributed, making information dissemination problematic. However, electronics can be used to provide mass distribution of information. Electronic information can be transmitted essential y at the speed of light and duplicated at minimal cost. Two electronic forms of information delivery will dominate in the 1990s: a satellite-based system and a wide-area computer network.

Satellite transmission of data has become a commonday occurrence for telephone and other communications. A geosynchronous satellite receives a transmission from Earth and rebroadcasts that message back to Earth over a wide area. Different frequencies are used to send multiple simultaneous messages. Two common modes of transmission are the Ku and C bands.

Interest in delivering agricultural information via satellite is growing. Several distance-learning programs have been developed at the University of Utah for delivery in Ecuador (13). Their developers are also preparing an undergraduate animal breeding and genetics class to be delivered over the national AG*SAT satellite instructional network, which routinely carries Extension programs. An Extension series of interactive dairy programs has been developed and delivered by the University of Washington (8) as well as by the University of Wisconsin (35). The American Farm Bureau also maintains a satellite link to 46 States and 573 of their county offices (72). This satellite link is used to transmit data as well as instructional programs.

Satellites not only make possible mass distribution of information, they do so in a way that makes this information easily accessible to end users. They only need a satellite reception disk and a television. However, development of satellite-based instruction programs can be expensive. Poor planning may also reduce attendance. Other problems include limited audience interaction and low motivation on the part of the end user to view the program. The importance of in-person interactions with the live speaker should not be underestimated. However,

Figure 4-6—Functional Components of the Crop Production Expert Advisor System



SOURCE: L.R. Maran, "CPEAS: The Crop Production Expert Advisor System," Knowledge Based Systems Research Laboratory, Department of Agronomy, University of Illinois, Urbana-Champaign, 1989.

if funds for education continue to dwindle, this may remain the only feasible means to conduct an Extension program.

Another method of rapidly delivering information is through a wide-area computer network. Much of the western world currently is criss-crossed with multiple computer networks. Two of the original computer networks are BITNET **(figure 4-7)** and ARPANET. BITNET was initiated at the City [University of New York and was used to connect major educational institutions. ARPANET was initiated by the Department of Defense. Today there are national computer networks for the government. commercial companies, and educational institutions. A number of regional networks have also been developed. These include networks such as Clemson University Forestry and Agricultural Network, CNET (Cornell University). and PENpages (Pennsylvania State University). Most of-these networks interface through the national Internet system so that messages can be sent from one network to another. Internet is funded by several government agencies and numerous companies (50).

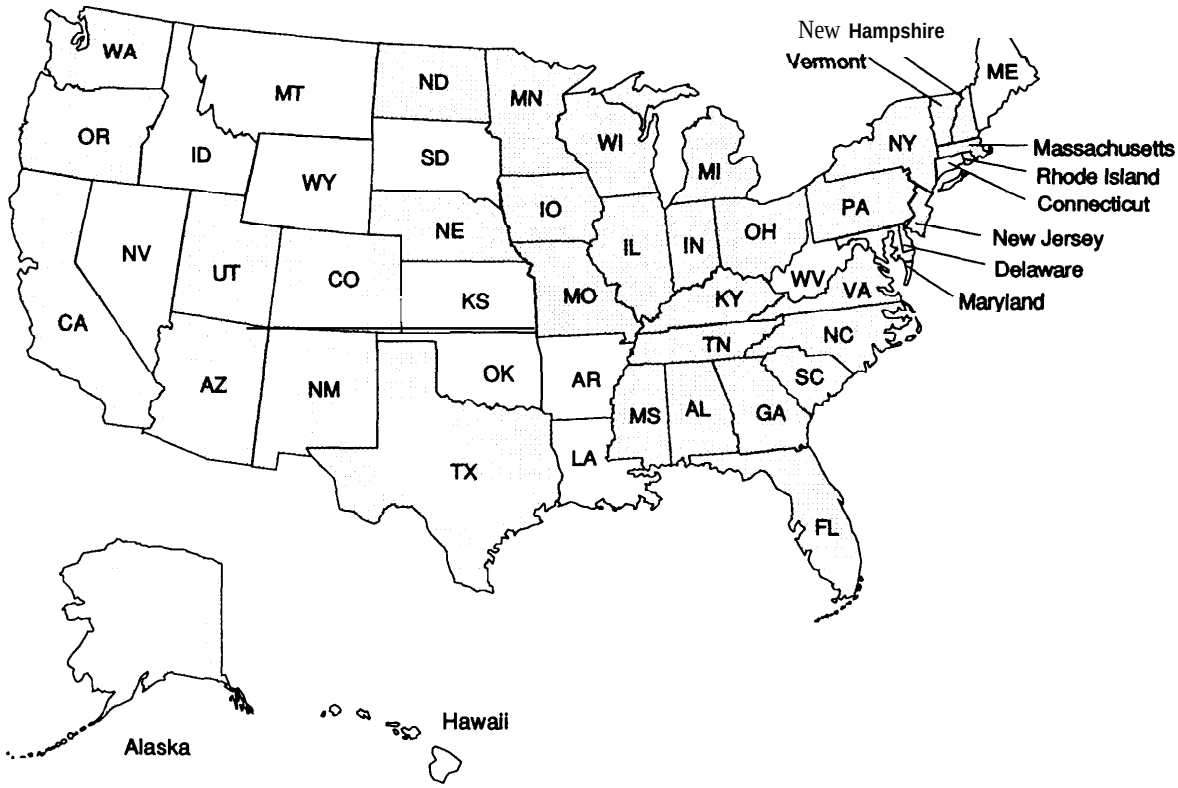
The main benefit of wide-area computer networks is the ability to rapidly share information and expertise. for instance, an industry situation report can be posted on the network and broadcast to all interested readers with access to the network. County Extension agents on the network can send and receive files in electronic format. In this way. interdisciplinary work can be conducted over long distances. Varner and Cady (103) have established a bulletin-board type system, called DAIRY-L, through which dairy professionals can request and receive information. DA IRY-L is only one of hundreds of bulletin-board systems, but a pioneer in the use of networking for Extension education.

DAIRY-L, which resides on the University of Maryland mainframe computer. was initiated early in 1990. Since that time subscription has grown to 150 subscribers from 37 states and 20 foreign countries (figure 4-8). Message traffic also has increased, approaching an average of 15 messages per month (figure 4-9). Messages are submitted to a ''list server' which in turn transmits them to all participants of DAIRY-L; therefore. all sub-

Figure 4-7—Topology of BITNET Connections in the United States

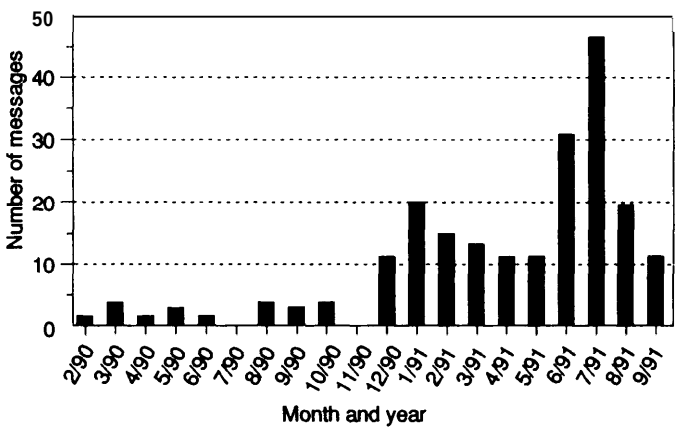
SOURCE: J.R. Lambert, '(Networks, Telecommunications and Multimedia Information Bases for Agricultural Decision Support, " commissioned background paper prepared for the Office of Technology Assessment, Washington, DC, 1990.

Figure 4-8—States with Participants in DAIRY-L.



SOURCE Mark Varner, University of Maryland (M.A. Varner and R A Cady. Dairy-L" A New Concept in Technology Transfer for Extension, *Journal of* Dairy Science 74(Supp 1): 201, 1991

Figure 4-9—Volume of DAIRY-L Messages.



SOURCE Mark Varner, University of Maryland (M A Varner and R A Cady. Dairy-L A New Concept in Technology Transfer for Extension, *Journal of* **Dairy Science 74(Supp. 1) 201, 1991**

scribers see all messages. Messages take the form of questions, notices, statements, and responses to previous mail. The list server also allows remote retrieval of files (figure 4-10).

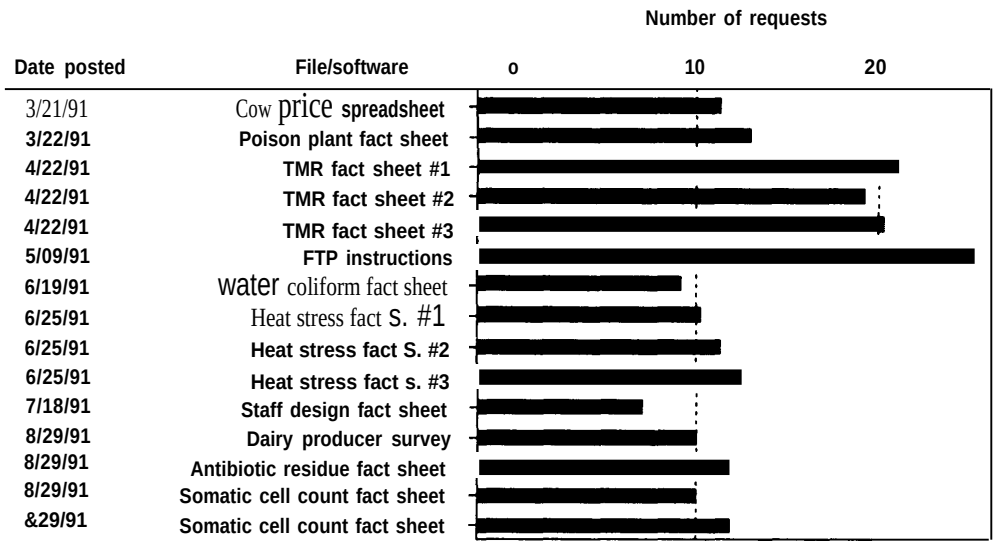
DA IRY-L has proven extremely useful to extension specialists needing knowledge in areas outside their institution's expertise. Because all members see all messages, DA IRY-L is also a powerful ediucational tool.

Information exchange through wide-area computer networks makes efficient use of personnel and resources. Therefore. a high priority should be given to maintaining and enhancing the backbone systems (i. e.. satellites and wide-area computer networks) that provide rapid dissemination of information. Since these systems are national in scope, this initiative should occur at the Federal level with USDA-ES providing the leadership in agriculture.

Robotics

Robotics are machines that can be programmed to perform a variety of labor intensive tasks in agriculture. Since 1968, when strew Dutch companies proposed mechanisms similar to robotics for harvesting citrus, researchers have proceeded though the poposal stage and currently are testing Laboratory and field prototypes for fruit harvesting. transplanting, tissue culture propagation. and machine guidance (67) (table 4- I).

Figure 4-10—Volume of DAIRY-L Requests for Remote Retrieval of Text Files and Software



SOURCE: Mark Varner, University of Maryland (M.A. Varner and R A Cady, 'Dairy-L A New Concept in Technology Transfer for Extension, Journal *of Dairy Science* **74(Supp. 1): 201, 1991.**

Most robotic applications under development are foreign-based. The United States is noticeably lacking in development efforts. Japan and Europe have much stronger programs and are likely to capitalize on this technology much sooner.

Agricultural robotics research is proceeding in two directions. One involves sensor technology (see following section) and machine vision. This is because, unlike production line robots, agricultural robots will operate in environments where interferences will be encountered. For example, a fruit-harvesting robot must be able to locate irregularly shaped fruit despite the obscuring effect of leaves and stems. A second research concern is robot end-effecters (i.e., grippers). These are the mechanisms through which robots conduct their work. Again, unlike industrial operations, agricultural robots will generally be working with fragile products (e.g., bedding plants and fruit). Touch and force feedback are necessary to avoid bruising or damaging plants, fruits, or animal products.

Three other areas of research are important for robot development but are not specific to agriculture. Manipulators are the physical linkages that move the end-effectors. Breakthroughs in speed and cost of manipulators are necessary. Agricultural robots will likely require less precision than industrial robots and will not require curvilinear motion, thus reducing the cost, Easily adopted robot components from nonagricultural applications would reduce the engineering costs of agricultural robots. A second research area is the development of computer algorithms for robot control. Significant advances in the miniaturization and integration of control hardware are needed. Integral feedback of the robot's position is essential. More powerful integrated circuit chips to interface sensors and to control the manipulators are also needed. New artificial intelligence approaches to task selection will be important facets of robot control research. A final area of research, systems simulation, allows evaluation of alternative robot configurations through animated computer simulations. Advances in computer simulation would reduce the development cost and time required in engineering a robot.

One major use of robots in agriculture will be for labor-**intensive tasks.** For example, there are two Dutch companies developing robots to milk dairy cows; one prototype is operating at the University of Maryland. Labor-saving robots will enable American farmers to remain competitive in world markets despite higher labor costs and a shortage of part-time, seasonal labor. They will also help to stem the flow of young, struggling industries such as ornamental horticulture, bedding plants, and plant tissue cultures to countries with low-priced labor. If robotics can help these industries survive, they will create or maintain jobs which would otherwise be lost.

Another major use of robots will be to micromanage crops. For example, a robot with an image sensor to detect weeds could be used to spot-spray herbicides. This

Table 4-l—A Partial Catalog of Research Applications of Robots in Agriculture

Application	Location	Notes
	Fruit harvesting	
Apple harvesting	France	Able to harvest 500/. of fruit
Citrus fruit harvesting	University of Florida	1 fruit every 3 seconds, able to harvest a fruit on 750/0 of its attempts
Tomato harvesting	Kyoto University	20 seconds per fruit
Cucumbers harvesting	Japan	In a laboratory study, the hand successfully completed the harvesting motion for 42 of 53 cucumbers.
Muskmelon harvesting	Purdue University Volcani Institute, Israel	5 seconds per fruit
	Plant material sensing and handling	
Transplanting		
• pepper plants	Louisiana State University	Transplanting rates as low as 1 plant every 3 seconds have been achieved with a 95°/0 success rate.
• marigolds and tomatoes	Purdue University	
• move plugs from one flat to another	Rutgers University	
Automated tissue propagation	University of Georgia, University of Florida, University of Illinois, New Zealand, Europe, Israel, Japan, Switzerland	Operations include retrieving the cuttings from a conveyor, trimming to size, stripping selected petioles, applying rooting hormones, and sticking the finished product into a plug flat cell.
Mushroom harvester	England	Uses a vision system to locate and size mushrooms and guide a selective robot harvester.
Forest thinning		Performs automatically selective felling within the tree ranks, bunching the harvested trees and carrying them to a process zone.
	Animal	
Robot milkers	Netherlands	
Sheep shearing	Australia	
Egg handling	University of California. Davis	Facilitated candle inspection,
Pork protein sensing	Purdue University	Robot moves an electro-magnetic scanner over a carcass.
Pork carcass sectioning	Sweden	
Oyster shucking	University of Maryland	Machine vision application to locate oyster hinges.
	Machine guidance	
Automated guided vehicles	Michigan State University Texas A&M University	Based on machine vision sensing.
Plowing robot	France	
Rice combine	Japan	Used edge-following to guide the machine around a rectangular field.
Direct spot spraying	Purdue University	Machine vision application to recognize plants.
Corn detasseling	Purdue University	Machine vision application to recognize plants

SOURCE Office of Technology Assessment. 1992

would encourage farmers to adopt conservation tillage and post-emergence spray programs.

Sensor Technology

Electronic systems use sensors to monitor their environment. Sensors will be used in data acquisition for computer systems such as expert systems and to assist robots to perform their tasks. Reliable sensors coupled with knowledge-basccl decision support systems will provide important managenment tools.

All data is collected through some kind of sensor. The human body has five (e.g., the sense of sight, touch, smell, hearing, and taste). However, there are substances that we are not able to directly sense (e.g., methane gas)

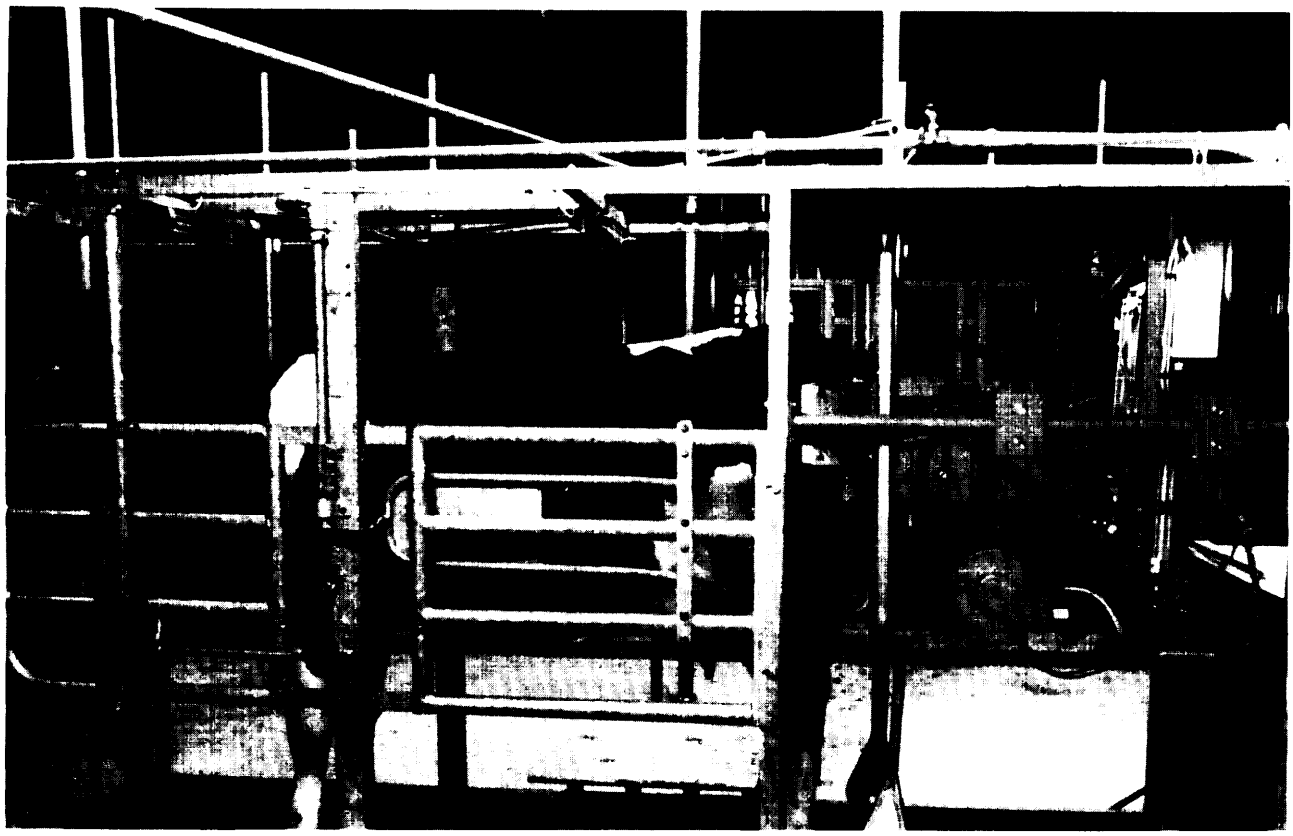
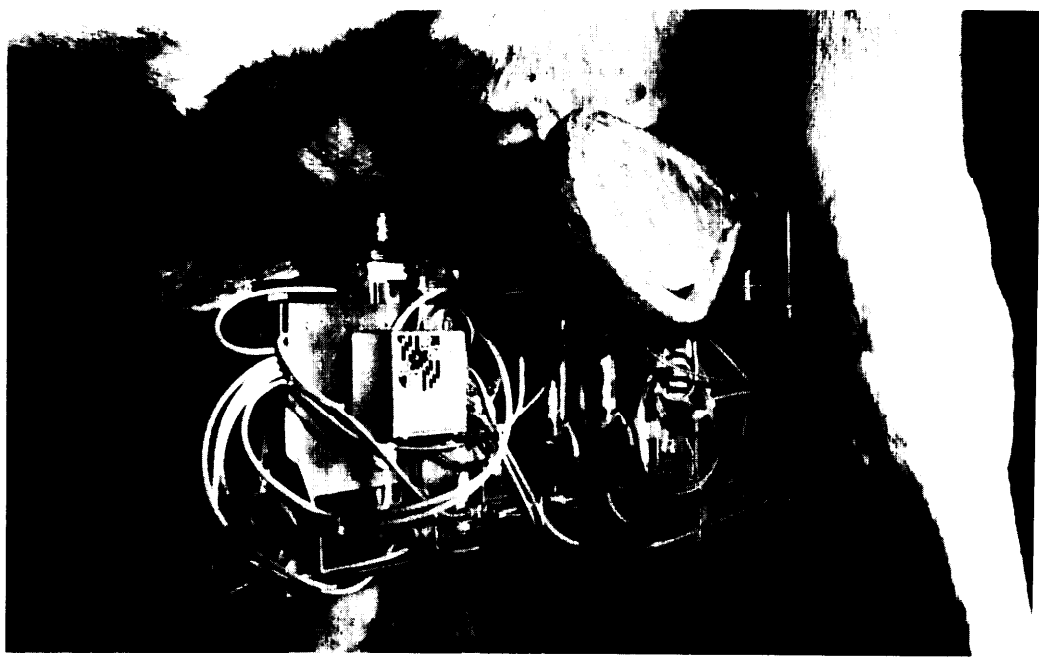


Photo credits: Norman Pruitt, Maryland Agricultural Experiment Stat/on.



This research prototype automated milking system, developed in the Netherlands, allows scientists to study system automation and robotics that can benefit dairy farms.

or that require more vigorous sensing than we can provide. Sensor technology provides information the human senses cannot access.

There generally are six classes of sensors. The newest is *machine vision* which processes images (e. g., camera input) to detect patterns. Nuclear *magnetic resonance* (NMR) is a noninvasive technique of resonating high-frequency electromagnetic radiation in the presence of hydrogen nuclei. This technology is widely used for diagnosis in the medical field, but it is costly and difficult to apply in field situations. *Neur-infrared (N/R) spectroscopy* is another noninvasive technique that measures the reflectance of NIR radiation by a substance. Because organic compounds absorb and reflect NIR radiation differently this is a quantitative sensor. *Acoustical measurements* provide another class of sensors for measuring the density of substances. *Biosensors* are sensors that incorporate a biologically sensitive material (e. g.. immobilized enzyme). *Electrical* sensors can monitor the electrical properties (e. g., conductance) of a substance.

Considerable work has been done in environmental sensing (i. e., crops, weather), somewhat less in animal sensing (i. e., estrus detection) (40). A partial list of research efforts in sensor technology is presented in table 4-2. Animal sensors are difficult to engineer due to biocompatability problems and animal welfare constraints.

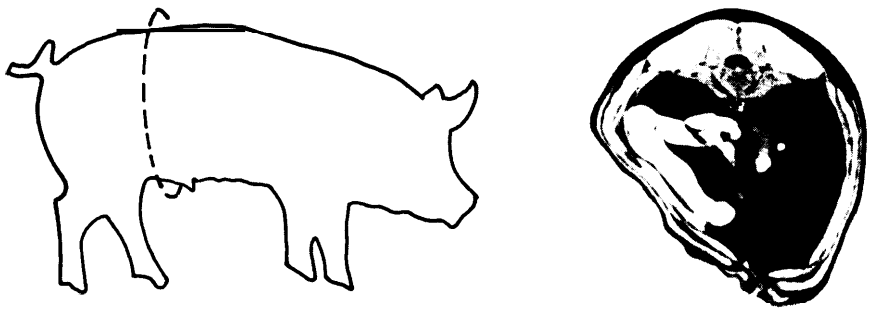


Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Drawing of pig (left) shows where cross section was made by magnetic resonance (MR) imaging. Spine, loin muscles, and kidneys are visible in upper part of MR image (right). Scientists can measure fat development under the skin quickly without injury to the pig.

Table 4-2—A Partial Catalog of Research Applications of Sensors in Agriculture

Application	Type of sensor
Electronic navigation system	Used the Global Position Satellite System
Automated plowing system	Photodetectors sensed the furrow edge
Tractor guidance	Computer vision
Monitor organic matter in soil	Light and NIR reflectance
Application of spray material	Electronic surface grid
Monitor gaseous ammonia	NIR spectroscopy
Moisture sensors for irrigation	Electrical resistance
Plant stress	Infrared leaf temperature sensor
Crop growth	Spectral reflectance
Weed identification	Machine vision
Identification of plant embryo shapes	Machine vision
Animal digestive system	Radionuclide imaging
Estrus detection	Electrical conductivity
Sex determination of baby chicks	Machine vision

SOURCE: Off Ice of Technology Assessment, 1992

Research on sensors for use in crop production generally focuses on the following objectives:

- Improving operations in crop production by machine guidance systems.
- Applying pesticide and fertilizer chemicals.
- Improving the management of irrigation water to conserve the resource and reduce production costs.
- Developing methods of monitoring crop growth to incorporate with computer models for improving day-to-day crop management and strategic planning.
- Developing sensors for assessing crop maturity and fruit location as basis for mechanical harvesting.

There remain numerous agricultural areas where sensors need to be developed (40). Doing so will require a multidisciplinary approach with input from professionals who understand the biology of the system in question as well as professionals who understand sensor technology (e. g., engineers and physical scientists). Some of the areas that need to be addressed include:

- Accurate three-dimensional fruit location sensor for crop canopies. This will facilitate robotic fruit harvesting.
- High-resolution navigation for field machines. Ability to program machine locations within inches, not several feet, is needed.
- A chemical drift sensor to monitor fertilizer and pesticide application and production of air polluting gases from animal units.
- Irrigation demand sensors that are not affected by soil properties and climatic factors.

Photo credit: Gerald Isaacs, University of Florida

An experimental fruit picking robot uses a machine vision sensor and a computer to locate individual fruit for detachment. Approximately 3 seconds per fruit are required.

- Animal stress sensors that can remotely detect early animal health problems.
- A fruit-ripeness sensor that can determine optimum harvest times and detect early stages of fruit and vegetable deterioration.
- Microbial sensors that can detect early development of spoilage or bacterial contamination in fresh meats, including poultry and seafood.

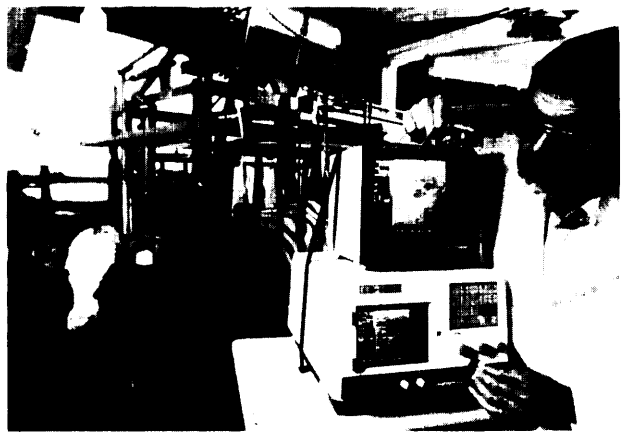


Photo credit: U.S. Department of Agriculture, Agricultural Research Service.

Animal physiologists test a sensor that will detect when this cow is ready to give birth.

An important component of the use of sensors in animal agriculture is telemetric data transfer and electronic identification of animals. For sensors that are to be implanted (e.g., tissue conductivity for estrus detection), telemetric data transfer must be accomplished within the size constraints which make implantation feasible. This remains a research issue. Implantable electronic identification systems have been developed and are currently under review by the Food and Drug Administration. Concern centers on the possibility that implantable sensors or identification units can enter the food chain.

The development of sensors will facilitate more forms of automatic control over various aspects of agricultural production. The development of robots is closely tied to success in the area of sensor technologies. A broader implication of sensor technology may be to provide a data acquisition system and a database from which decision support systems can operate. This should result in tighter controls for management and higher profitability for the enterprise. Another important impact of sensor technology will be in the food safety arena. Sensors to detect food spoilage or contamination will greatly increase the safety of the American food supply.

SUMMARY/PROGNOSIS

Computer technologies change at such a rapid pace that it is difficult to foresee their application in the next decade accurately. Irrespective of agricultural policics. computer technologies will continue to advance to support the needs of other industries. Meanwhile. a number of impendiments exist that are likely to slow adoption of these technologies in agriculture. These impediments can be removed through changes in policy. Most projections of agricultural application of computer technologies have been overly optimistic. For example, Holts futuristic view of the application of computer technoolgies for farm management (38) is still 20 years from fruition.

OTA has developed a scenario for the application of computer technologies in agriculture assuming that new technologies have a 5-year development phase. That is to say that once a research project begins it takes 5 years before that technology is applied. It was also assumed that incentives to bring new computer technologies out of the research laboratory and into production agriculture would exist. There are almost no incentives to do so today . Thus. American agriculture will not be affected by these technologies in a major way for at least10 years.

The Current State

By and large. computers have had little impact on production agriculture to date. Predictions that every farmer would own a computer by 1990 have not come true. Few farmers have computers and those who do use them primarily for bookkeeping and routine calculations (e. g.. ration balancing).

Computers have had somewhat more impact on agriculture support industries. Using computer networks and tracking systems. equipment dealers are better able to provide faster service and feed dealers are better able to manage feed inventories. Most of these advances have come from directly adopting general business software with little or no input from the agricultural academic community.

Another technology that currently is being adopted by farmers is fax machines. This allows for rapid exchange of printed material. An example of the use of this technology is in ration balancing. A nutritionist can receive the results of a feed analysis by fax from the laboratory. formulate a ration. and fax that to the farmer all with-in a few minutes. There is limited use of networks for exchange of information among Extension personnel (i .e , Dairy-L) and among protoype full-text databases (i. e., National Diary Database).

Mid-1990s

Within the next few years. many technologies currently under development should find their way into application. By the mid 1990s, the performance of microcomputers will likely double, eroding some of the current constraints to farmer adoption of computer tech nology. However. it still is unlikely that a high proportion of farmers will own a personal computer by that time.

The primary application of advanced computer technology in the mid-1990s will be in the form of ad hoc expert systems to solve well-defined problems. These will be primarily problem diagnosis expert systems that are currently under development. Farmers will have a cadre of expert systems at their disposal to diagnose diseases and to evaluate animal and crop performance. These systems will generally not be integrated with each other and each will condisider one aspect of a problem. Integrated systems that solve producton problems while considering economic consequences will not become available until later in the decade.

The primary use of expert systems within the next 5 years may be by agribusiness personnel, as they will be able to leverage the cost of' adopting these technologies across more farms. Using expert systems to provide additional service to farmers may cause a shift in the role of some professionals. For example. expert systems help veterinarians take an epidemiological approach to solving problems (85). It will also cause some diversification in services provided. For example. nutritionists may be more likely to become involved in consulting for the crop program when armed with an expertsystem.

Sensors will see limited application for collecting real-time data for expert systems. The primary use of sensors will be for monitoring weather and field conditions for crop management. Expert systems will help farmers to interpret these data and suggest appropriate management strategies such as irrigation, fertilization, or pesticide treatment.

Another technology likely to see application within the next 5 years is full-text retrieval systems. It will be possible for farmers and Extension personnel to have a CD-ROM with all of the latest publications at their fingertips. Using a full-text retrieval system they will be able to retrieve pertinent information that will help them make better decisions. For example. when a farm experiences a corn mycotoxin problem, the manager can access an information base to find relevant literature. Large information bases, such as the national dairy database, will likey be developed and delivered by 1995.

Robots for highly specialized, labor-intensive tasks will begin to be applied to agriculture in the late 1990s. This would include robot transplanting of seedlings and pork carcass sectioning. Robots for milking cows could reach application by the mid- 1990s.

2000

The turn of the century should bring with it significant new applications of computer technologies in American agriculture. Ten years will provide sufficient time for the acceptance by farmers of computer technologies as a valid management tool and for the development of integrated management programs. It will also allow time for universities to become comfortable with these technologies and for personnel to be properly trained in developing these technologies.

By 2000, whole-farm advisors, or integrated "management workstations, should be developed. A management workstation will consist of integrated decision support tools with a multimedia presentation of information. The workstation can thus serve as a diagnostic tool, an information source, an advisor, and a planning system. The expert systems will consider the holistic view of an enterprise when making recommendations. The systems will also share data so that information used in one system will be available to other systems. This generation of expert systems should operate as monitors that can alert producers to potential problems, as opposed to current expert systems which are situation-driven: that is, the producer must perceive a problem and decide to execute the system. The management workstation will also contain an advanced user interface consisting of speech recognition and touch-sensitive screens.

The future dairy management workstation might contain decision support systems that monitor the financial records, the herd production records and the crop production records. Cropping decisions would be integrated with the dairy needs, the financial situation, and the land resources available. Currently, these decisions are all made independently. When the farmer is alerted to a problem (e. g., pest infestation). he or she can use the multimedia features of the workstation to retrieve video segments to learn how to identify the pest and the proper techniques for applying a pesticide.

Robots for harvesting fruits and vegetables and for automatically guided vehicles should become available by 2000. Their application will depend on the cost associated with using human labor for the same job.

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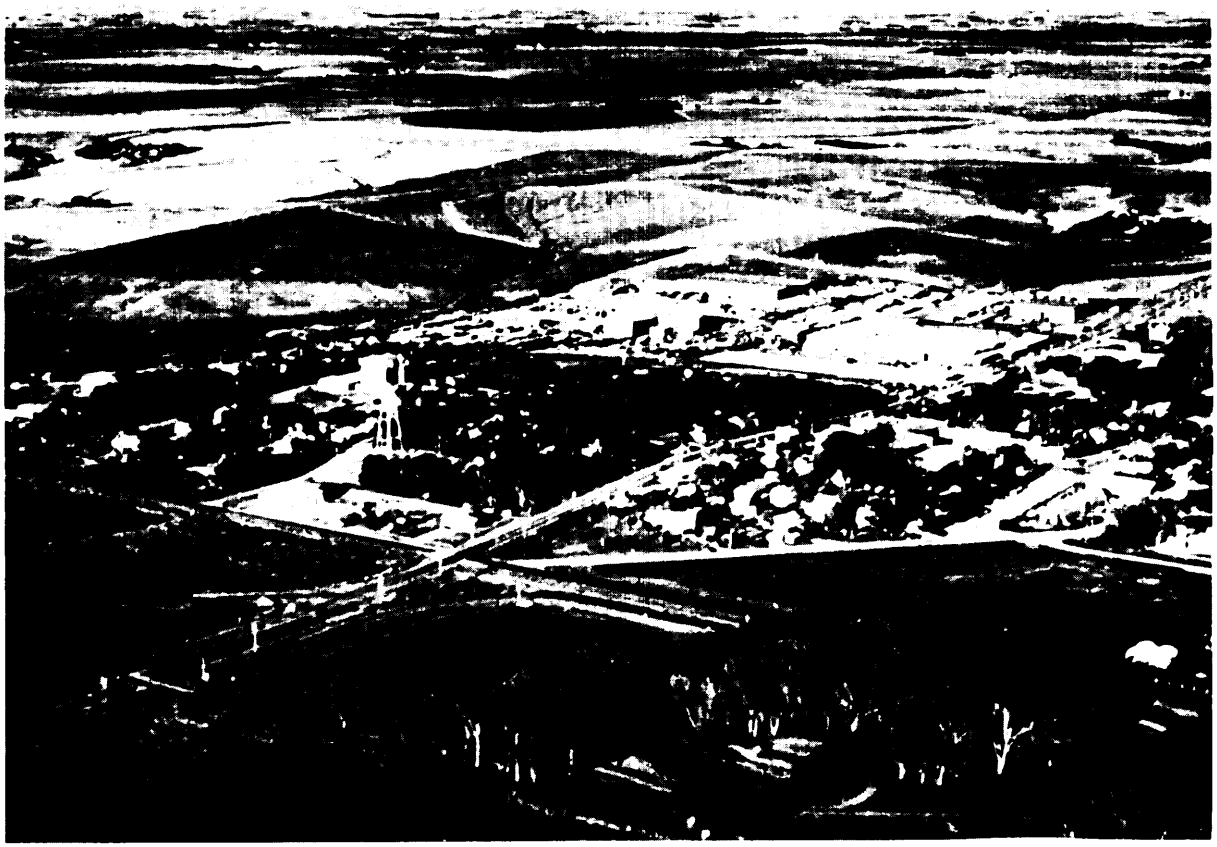
Part II

Implications of New Technologies for Agricultural Production

Chapter 5

Productivity Implications of New Technologies



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Chapter 5
Productivity Implications of New Technologies

Technologies discussed in the preceding chapters have the potential to increase American agricultural productivity, enhance the environment, improve food safety and food quality, and help increase U.S. agricultural competitiveness. Many of these technologies are fast approaching commercialization. Research in crop agriculture has advanced at a much faster pace than anticipated just a few years ago. Much of the research is aimed at improving crop resistance to weeds, insects and diseases: geoclimatic adaptation; and quality characteristics. In animal agriculture, new vaccines and diagnostics are on the market or soon will be. Growth promotants are going through the regulatory process. Reproduction technologies are advancing at a rapid pace and cloned embryos are currently being marketed. Transgenics are still in the future, but considerable strides are being made in the use of livestock to produce high-value pharmaceuticals.

The advance of agricultural biotechnology and computer technologies will play an important role in increasing agricultural productivity and accelerating structural change in agriculture. These technologies, however, are not magic—a high degree of management skill will be needed to capitalize fully on their potential benefits. It will be important to develop management systems that make the most effective use of these technologies. This chapter and chapter 6 address these issues. In this chapter the technologies' impacts on productivity are analyzed and implications for the agricultural industry are discussed. In the next chapter management issues will be examined.

TECHNOLOGY ADOPTION AND PRODUCTIVITY IMPACTS: NEW PROJECTIONS

OTA conducted two workshops—one for animal agriculture and the other for crop agriculture—in part to assess the impacts of these emerging technologies on agricultural productivity. Workshop participants, carefully selected to include those with expertise in different stages of technological innovation, included physical and biological scientists. engineers, economists, extension specialists, commodity specialists. representatives from agribusiness and public interest groups, and experienced farmers.

The workshop participants were provided state-of-the-art papers on each technology prepared by leading scientists in the respective areas. These papers provided data on: 1) timing of commercial introduction for each technology area; 2) net yield increases (by commodity), expected from the technologies; and 3) number of years needed to reach various adoption rates (by commodity). The Delphi technique' was used to obtain collective judgments from each workshop participant on the development and adoption of the technologies.

Timing of Commercial Introduction

Workshop participants were asked to estimate the probable year of commercial introduction of each technology under three alternative scenarios/environments assumed to extend to the year 2000:

1. Most likely scenario—a) a real rate of growth in research and extension expenditures of 2 percent per year, and b) continuation of all other forces that have shaped past adoption of new technology.
2. More new technology scenario (relative to the most likely scenario)—a) a real rate of growth in research and extension expenditures of 4 percent annually, and b) all other factors more favorable to new technology adoption than those of the most likely scenario.
3. Less new technology scenario (relative to the most likely scenario) -a) no real rate of growth in research and extension expenditures, and b) all other factors less favorable to new technology adoption than those of the most likely scenario.

Table 5-l shows in more detail the sets of assumptions made under the alternative scenarios. Table 5-2 shows workshop participants' estimates of the probable years of commercial introduction of animal technologies, and table 5-3 shows the same for crop technologies under the three alternative scenarios.

[1] The Delphi technique is a systematic procedure for eliciting and collating informed judgments from a panel of experts. It has distinctive feedback characteristics. During the Delphi process, responses are collated and made available to the experts for review. Each expert reevaluates his or her original answer after examining the group's response. The iterative process of evaluation, feedback, and reevaluation continues until a consensus is reached. Since this is not a random sampling, the results obtained through the Delphi process depend heavily on the experts selected.

Table 5-l—Alternative Technology Scenarios

Factors	More new technology	Most likely technology	Less new technology
Population growth rate			
U.S	1.0%	0.7%	0.5%
World	1.8%	1.6%	1 .3%
GNP growth rate			
U.S	4%	3.4%	3.0%
World	5%	3.5%	2.0%
Trade policy	Less protectionist, more favorable terms of trade	Continuation of present policy	More protectionist, less favorable terms of trade
Tax policy	More favorable toward technology development	Continuation of present policy	Less favorable toward technology development
Rate of growth of export demand			
Grain	1.8%	1.4%	.8%
Oilseeds	2.3%	1.8%	1 .2%
Red meat	2.0%	1.0%	O.O%
Energy price growth rate (constant dollars)	5%	3%	1%
Growth rate of research and extension expenditures (constant dollars)	4%	2%	00/0
Inflation rate	8%	5%	30/0
Regulatory environment	Less regulation, more favorable climate for technology development	Continuation of present policy	More regulation, less favorable climate for technology development
Consumer acceptance of new technology	High	Moderate	Low

SOURCE: Oftice of Technology Assessment 1992

These estimates range from the very near term for genetically engineered growth promotants and animal health technologies to 2000 and beyond for transgenic animals and certain crops. Participants thought that many of the advancing technologies may be available by the mid- 1990s. Of the 41 potentially available animal technologies, 21 were estimated to be available by 1995 under the most likely scenario. In crop agriculture, 19 of the 30 technologies examined were projected to be available for commercial introduction by 1995.

Primary Impacts

When technologies are adopted on farm their immediate technical impact on crop agriculture is usually increased yields, a changed product characteristic, and/or increased percentage of planted acreage harvested. For animal agriculture the impact is on feed efficiency for all animals, reproductive efficiency for beef cattle and swine, milk production for dairy cows, and the number of eggs per layer (producing hen) for poultry.

To estimate the net impact of emerging technologies on agricultural production, workshop participants, using information provided about the new technologies at the meeting, projected net increases in crop yields, animal feed efficiencies, and other performance measures that could be expected if the technologies were commercially available and fully adopted by farmers (i.e.. adopted by all farmers). Since in practice most technologies would be used in combination with other technologies (including existing technologies), the individual technologies were grouped by the workshop participants according to their probable impacts on particular commodities under different scenarios. The commodities included corn. cotton, soybeans, wheat, beef cattle, dairy cattle, poultry, and swine. Through a Delphi process. OTA obtained estimates for each package of technologies on each of the commodities under the three alternative scenarios.

Adoption Profiles

When a new technology is introduced into the marketplace, only a small number of farms, mostly the large and innovative ones, will adopt the technology initially. This is because the possible payoff of the new technology is uncertain and because potential adopters need time to learn how to use the new technology and evaluate its worth. As early adopters benefit from using a new technology. more and more farmers are attracted to it, increasing the speed of adoption exponentially. Eventually. as most farmers who will adopt a new technology do so, the adoption rate will level off. Thus, the adoption profile follows an S-shaped curve (2).

Table 5-2—Timing of Commercial Introduction of Advancing Animal Technologies

Technology	Technology scenarios		
	More new technology	Most likely technology	Less new technology
Somatotropins			
Bovine:			
Dairy	1991	1991	1991
Beef	1995	1997	2000
Pork:			
pas t	1991	1992	1995
GRF	1994	1995	1998
Poultry:			
Broilers	1998	2000	>2000
Turkeys	1998	2000	>2000
Beta-agonists	1991	1992	1995
Reproduction and embryo transfer			
Control of ovarian functions	1993	1995	1995
Separation of X&Y bearing sperm	1992	1995	1995
In vitro fertilization	1990	1990	1990
Embryo sexing	1998	2000	>2000
Cloning and nuclear transfer	1993	1995	1995
Gene transfer	2000	>2000	>2000
Animal health			
rDNA technology	1991	1993	1995
Gene deletion	1991	1995	1995
Monoclinal antibodies	1991	1995	1995
Peptides	1994	1996	>2000
Immunomodulators	1994	1996	>2000
Antibiotic growth promotants	1990	1990	1990
Steroid-like growth promotants			
Estrogen/androgen combinations	1990	1990	1990
Controlled/sustained release	1990	1990	1990
Transgenic			
Ruminants:			
Hormonally enhanced growth	2000	>2000	>2000
Pharmaceutical production	2000	>2000	>2000
Enhanced disease resistance	2000	2000	>2000
Poultry	>2000	>2000	>2000
Swine:			
Improved productivity	2000	>2000	>2000
Disease resistance	2000	>2000	>2000
Disease immunity	2000	>2000	>2000
Fish:			
Rapid growth...	1995	2000	>2000
Disease resistant	1995	>2000	>2000
Expert systems	1992	1995	2000
Human-computer interactions			
Add-on systems	1992	1995	2000
Integrated systems	1995	2000	>2000
Sensor technology/robotics			
Reproduction	1992	1995	1998
Health,	1995	2000	>2000
Stress	1998	>2000	>2000
Carcass evaluation	1992	1995	1998
Milking system	1994	1995	1998
Environment and animal behavior			
Optimizing environmental stimuli	1992	1995	>2000
Stress and immunity	1993	1995	2000
Cognitive processes	1995	2000	>2000
Facilities and equipment	1992	1994	1996

SOURCE Office of Technology Assessment 1992

Table 5-3-Timing of Commercial Introduction of Advancing Crop Technologies

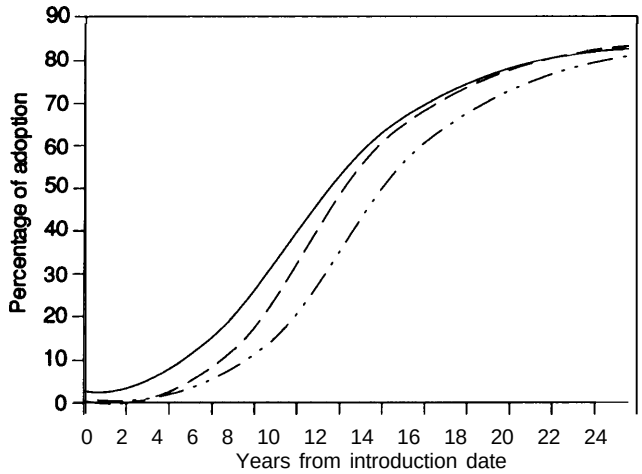
Technology/problem area	Technology scenarios		
	More new technology	Most likely technology	Less new technology
Pest control			
Pathogens for insect control:			
rDNA - microbial insecticides	1993	1995	>2000
Introduction and colonization/rDNA	1998	>2000	>2000
Use of parasites/predators	1998	>2000	>2000
Genetic modification for resistance to insects:			
Bacteria	1992	1995	>2000
Viruses	1993	1995	>2000
Plants	1995	1998	>2000
Insect and mite management	1990	1990	1990
Weed control			
Biocontrol for weeds:			
Host specific pathogens	1995	1998	>2000
Bioherbicides	1991	1995	>2000
Anthropoids	1997	2000	>2000
Genetic modification for weed control			
Herbicide tolerance	1993	1995	2000
Allelopathy	>2000	>2000	>2000
Disease control			
Microbial biocontrol of plant diseases:			
Manipulation of resident microbial communities	1993	1997	>2000
Antagonistic organisms	1993	1997	>2000
Genetic modification for disease resistance	1995	2000	>2000
Disease management:			
Crop loss assessment	1991	1995	2000
Cropping system/agroecosystem interaction	1990	1990	1990
Plant stress			
Temperature and water stress:			
Biochemical/physiological indicators	1995	2000	>2000
Genetic modification	2000	2000	>2000
Root responses to stress	2000	2000	>2000
Detection of stress	1991	1995	2000
Information technology			
Knowledge-based systems for crops:			
Farm-level planning systems	1991	1993	1998
Information networks	1993	1995	2000
Expert systems for business decisionmaking	1990	1990	1990
Networks/telecommunications:			
Commercializing public databases	1992	1995	2000
Private databases	1992	1995	2000
Commercializing public software	1992	1995	2000
Private software	1992	1995	2000
Robotics:			
Plant materials sensing/handling	1993	1995	1998
Machine guidance	1994	1997	>2000

SOURCE: Office of Technology Assessment, 1992.

Many factors go into the decision to adopt a new technology. A factor of growing importance is the ratio of consumer acceptance to rejection of a new technology. For example, it is likely that a portion of the population will prefer to purchase products that have been produced without the use of growth hormones. The size of this market segment is difficult to estimate, but it will probably support some producers who do not adopt hormones.

Other biotechnology products, suchas improved disease vaccines. most likely can be implemented effectively by most producers and will have fewer new

Figure 5-l—Logistic Adoption Curves for Corn, Package A



SOURCE" Off Ice of Technology Assessment

management requirements than recombinant somatotropins. The extent to which such innovations are commercialized and adopted will depend on their profitability and effectiveness compared to that of other available technologies.

To derive an adoption profile for each package of technologies under different scenarios, workshop participants were divided by expertise into commodity groups. There were four groups in the animal technology workshop (beef, dairy, poultry, and swine) and four in the crop technology workshop (corn, cotton, soybeans, and wheat). The participants were then asked the question, ‘ ‘If a specific package of technologies was introduced in the market today, how long would it take for farmers to adopt it’?’ Based on their answers, a logistic curve depicting the rate of adoption was fitted for each package of technologies applied to the eight commodities under different scenarios (see example in figure 5-1).

Projection of Animal and Crop Production Efficiencies

Based on information obtained from the workshops on: I) years to commercial introduction, 2) primary impacts by technology package, and 3) adoption profile, OTA computed ‘‘performance measurements” for the eight commodity areas by the year 2000 under alternative scenarios. The results are presented in tables Table 5-4 and 5-5.

Under the most likely scenario, feed efficiency in livestock production will increase at an annual rate of from 0.39 percent for dairy to 1.62 percent for swine. In addition. reproduction efficiency will also increase, at an annual rate ranging from 0.67 percent for beef cattle. to 1.25 percent for swine. Milk production per cow per year will increase at 3.01 percent per year. from 14,200 pounds to 19,200 pounds per cow, in the period 1990–2000.

During the same period, major crop yields are estimated to increase at rates ranging from 0.39 percent per year for soybeans to 2.02 percent for wheat. Wheat yield, for example, is projected to increase from 34.8 bushels per acre to more than 42 bushels per acre in 2000 under the most likely scenario.

How do these rates of increase compare with historical trends and with OTA’s last projections (8)? The most dramatic productivity increase is in milk production with a 3-percent annual rate of growth. Since 1960. the annual rate of growth has been about 2.5 percent. However, OTA’s 1985 projection (24,200 pounds of milk per cow by 2000) was higher than its current one (19.200 pounds of milk per cow by 2000). A major reason for this discrepancy is the delay in marketing of bovine somatotropin. In 1985 it was predicted to be commercially available in 1987. As of early 1992 it has yet to be approved. In addition, the high milk yields projected in 1985 were revised downward in 1990 as more knowledge about the bST technology became available through additional research.

Further increases in feed efficiency in livestock will lag behind historical trends in some cases and surpass these trends in others. Poultry feed efficiency has been increasing at about 1.2 percent per year for the past decade. This has resulted in making the chicken an extremely efficient converter of feed to meat. Further increases in feed efficiency will be difficult. Feed efficiency will continue to increase at 0.5 percent per year to 2000 under the most likely scenario. Feed efficiencies for beef and swine, on the other hand, have been static for the last decade. New technologies will increase feed efficiencies. Under the most likely scenario. feed efficiency for beef is projected to increase at an annual rate of 0.74 percent, reaching 0.154 pounds of beef per pound of feed in 2000; feed efficiency for swine will increase at the rate of 1.62 percent per year, reaching O. 18 pounds of

Table 5-4—Estimates of Crop Yield and Animal Production Efficiency by 2000

	Actual 1990	Less new technology 2000	Most likely technology 2000	More new technology 2000
Crops				
Corn—bu/acre	116,2	113.8	128.5	141.6
Cotton-lb/acre	600.0	NA	708.0	NA
Soybeans—bu/acre	32.4	32.6	33.7	36.4
Wheat—bu/acre	34.8	37.7	42.6	53.8
Beef				
Lbs meat/lb feed	0.143	0.146	0.154	0.169
Calves/100 cows	90.0	93.750	96.221	102.455
Dairy				
Lbs milk/lb feed	1.010	1.030	1.050	1.057
Lbs.milk/cow/year	14,200.0	17,247.200	19,191.600	20,498.800
Poultry				
Lbs meat/lb feed	0.370	0.373	0.389	0.428
Eggs/layer/year.	250.0	250.500	258.0	273.125
Swine				
Lbs meat/lb feed	0.154	0.174	0.181	0.196
Pigs/sow/year	13.900	14.420	15.750	17.791

NOTE" OTA expresses its appreciation to Yao-chi Lu and Phil Calling, Agriculture Research Service, U.S. Department of Agriculture for their assistance in deriving the estimates for this table.

NA = Not available.

SOURCE: Office of Technology Assessment, 1992.

Table 5-5—Projected Annual Rates of Growth (1990-2000)

	Less new technology	Most likely technology	More new technology
Corn	–0.21%	1.00%	1.97%
Cotton	NA	1,66	NA
Soybeans	0.06	0.39	1,16
Wheat	**0.80**	**2.02**	**4,36**
Beef			
Lbs meat/feed	**0.21**	**0.74**	**1.67**
Calves/cow	**0.41**	**0.67**	**1.30**
Dairy			
Lbs milk/feed	**0.20**	**0.39**	**0.46**
Milk/cow/year	**1.94**	**3.01**	**3.67**
Poultry			
Lbs meat/feed..	**0.08**	**0.51**	**1.46**
Eggs/lay/year	**0.02**	**0.32**	**0.89**
Swine			
Lbs meat/feed..	1.22	1.62	2.41
Pigs/sow/year	0.37	1.25	2.47

NOTE: OTA expresses its appreciation to Yao-chi Lu and Phil Coiling, Agriculture Research Service, U.S. Department of Agriculture, for their assistance in deriving the estimates for twistable.

NA = Not available.

SOURCE: Office of Technology Assessment, 1992.

pork per pound of feed in 2000. OTA made the same projection in 1985.

Efficiencies in crop production will about match historical trends or climb slightly, and for the most part will exceed OTA's 1985 projections. This, in part, reflects the movement of many of the new technologies from the laboratory to the field at a much quicker pace than thought possible in the mid-80s. For example, in 1985 OTA projected wheat yields to increase at an annual rate of 1.2 percent under the most likely scenario. In the early 1990s they are projected to increase at a rate of 2 percent to the year 2000. Cotton was expected to increase at an annual rate of 0.7 percent in the mid-80s, but now is projected to increase at a rate of 1.66 percent to the year 2000. Soybeans are the exception. They were projected to increase at a rate of 1.2 percent in the mid-80s but now are projected to increase at the more modest rate of 0.39 percent, in part because biotechnology products are projected to become available to the soybean industry more slowly than previously thought. Note that corn is expected to decline from actual 1990 yield under the less-new technology scenario. This is due, in part, to the anticipated loss of existing chemical technologies and a very slow rate of new biological technologies to replace them.

Even though annual rates of growth in many agricultural products may accelerate during the 90s. the absolute

quantity of yields will, for the most part, be lower than projected in the mid-80s. This is due, in part. to the fact that many of the early biotechnology inputs will be substitutes for chemical inputs and, hence, the absolute gain in productive efficiency will in many cases be negligible. This is expected to improve in the latter part of the decade as more is learncd about the genetic makeup of plants.

IMPACTS OF NEW TECHNOLOGIES ON THE STRUCTURE OF CROP AGRICULTURE

Production agricultural commodities generally fit into two categories: large-acreage volume crops. such as wheat, corn. and soybeans: and less volume small-acreage specialty crops, such as tomatoes, potatoes, and onions. There are several important distinctions between the two categories.

First. there is less verticul integration of input, production, and marketing stages for large-acreage volume crops than for some small-acreage specialty crops. Second. the potential market for new technologies is much greater for large acreage crops than for specialty crops. This is an important driving force in terms of technoigical innovations. Third, biotechnology processes are already available to alter the harvestable component of some specialty crops such as tomatoes. This is due. in large part. to the fact that many specialty crops are easier to manipulate genetically than food and feed grain crops. Such developments are for the most part further away for the major food and feed grain crops (5).

Large-Acreage Volume Crops

As discussed in chapter 2, biotechnology i.implications such as herbicide resistant plants and biopesticides should be available in the near future. Unlike previous mechanical technologies. most biotechnologies will not, in themselves. generate significant economies of size. Also. there appears to be lttlc incentive for firms supplying seed and chemical inputs to expand vertically into crop production. Biotechnololgies that increase yield will have supply-increasing, price-dampening effects. These will adversely affect the survival of high-cost producers. which for the most part are small to moderate-size farm operations.

Small-Acreage Specialty Crops

As indicated in chapter 2, biotechnology already has the capability to modify the harvestable product for some specialty crops. This capability will increase the extent to which processes specify product quality. It will also provide an incentive for vertical coordination between production inputs and the production and processing stages for a number of specialty crops. Thus, even though there are no obvious economies of size to be captured with biotechnology innovations, these innovations will facilitate vertical coordination in some cases. Small producers will be at a competitive disadvantage in specialty crops markets unless they have a particular market niche (5).

For fruits and vegetables, biotechnologies will be important where product quality, shelf life, and taste are important characteristics. Technologies that allow for greater selectivity in specifying performance characteristics of different crop varieties will allow more rapid development of desirable cultivars and much more rapid propagation of plant stocks. Markets for tomatoes, let-

Photo credit' Grant He//man, Inc.

Advancing technologies will have supply-increasing, price-dampening effects on large-acreage volume crops such as wheat. This will adversely affect high-cost farming operations.

B g

tuce, and carrots are large and relatively focused on a few specific varieties. Improvements in these crops have the potential for rapid and widespread adoption to the benefit of growers, plant stock breeders, and consumers. There will be significant price differentials connected to biotechnology-based improvements and consumers can expect to pay higher prices for products more tailored to specific segments of the market.

New Crops and New Uses of Existing Crops

Biotechnology offers great potential for developing new crops and/or modifying existing crops for food, feed, and industrial uses. Examples include the modification of seed composition of corn and soybeans.

Industrial use of corn for glucose, dextrose, starch, and alcohol has expanded rapidly, and biotechnology offers the capability to modify the protein, starch, and oil content of grain. Currently in the United States, approximately 3 percent of corn acreage is planted to special-use hybrids such as white corn for corn meal and grits, waxy corn for use as thickeners in the food industry, and hard yellow corn for snack chips. The other 97 percent is sold under the broad market classification of No. 2 yellow corn, without measurement of protein, starch, or other quality characteristics (6).

For it to be economically feasible for farmers to grow products such as special-use corn hybrids, they must be able to capture price-premium incentives for these products. The current marketing system cannot easily accommodate new market channels for special varieties. It is expected that direct contracting between processors and growers will play an important role in the market development and growth of special-use products.

The above example for corn hybrids suggests the likely pattern for marketing of other special-use crops. Where specialty market niches are small, incentives for a high degree of vertical integration in production and marketing will be substantial. This will limit the production opportunities for most independent producers (5).

IMPACTS OF NEW TECHNOLOGIES ON THE STRUCTURE OF ANIMAL AGRICULTURE

The U.S. livestock industry is divided into two components. One is increasingly space-concentrated, higher technology, and intensively managed. This component includes specialized cattle feedlots, broiler and swine production under confinement, and some large, highly specialized dry-lot dairy operations. A second component is the range livestock sector, which includes a large number of beef cow-calf operations along with a variety of small, lower technology livestock farms, many of which are operated by part-time farmers.

A number of biotechnology applications is expected to have rather high adoption rates within the higher technology component of the livestock sector, compared to the lower technology, spatially dispersed sector. This is due, in large part, to the fact that increased managerial expertise is needed to use these new technologies effectively; such expertise tends to be associated with confinement systems.

Growth promotants will be the first major biotechnology products to be made available to U.S. agriculture. The dairy and pork sectors will be the first to make use of these technologies.

Case Studies

Dairy Sector

The dairy industry will most likely be the first to adopt technologies from the biotechnology era of the 1990s,

Photo credit: Grant Heilman, Inc.

In the dairy industry the trend toward fewer and larger farms has been on-going for decades. The trend will accelerate as a result of new cost-reducing technologies and a more market-oriented dairy policy.

and also will feel the first profound impacts of the emerging technologies. Biotechnology advances in reproductive technologies. animal health technologies, and growth promotants will make major contributions to the sector. In particular, bovine somatotropin (bST), a growth promotant, will significantly increase milk production. Bovine somatotropin is a naturally occurring hormone that increases milk yield in the dairy cow. Its effect has been known for decades but until it could be produced by rDNA procedures, it was not economically viable. This technology will increase milk yield per cow in 1 year to what it would take 10 to 20 years to achieve with current reproductive technologies (7).

The economic effects of these emerging technologies can be visualized by analyzing the impacts on different sized farms in different regions. Representative farms used in the analysis are briefly described in table 5-6. Once bST becomes available, strong incentives will exist to adopt the technology. Payoffs from bST adoption are substantial, regardless of region (see table 5-7). Nonadopters of bST will have more problems surviving and will be more likely to exit the industry.

Regional shifts in milk production patterns are expected for several reasons (tables 5-8 and 5-9). Upper Midwest farms have problems realizing sufficient earnings to achieve a reasonable return on equity, compete. and survive. While Northeast farms fare better, they too were found to be at a disadvantage relative to Pacific and Southeast farms. In all regions, adoption of bST increases the potential to survive, especially for larger farms.

Concern that bST will force many dairy farms out of the industry, especially in the traditional milk-producing region of the Upper Midwest and Northeast, has helped make this new technology the center of controversy. BST alone, however, will not force these traditional farms out of existence. The trend toward fewer total cows and larger farms has been underway for many decades. This trend is the result of a combination of emerging technology. economies of size, and policy. The trend will no doubt accelerate in the 1990s as the result of a combination of bST and other cost-reducing technologies, and a more market-oriented dairy policy. Such changes inherently put increased pressure on smaller traditional dairy farms. These pressures are accentuated by technological change but they are not new. For a more extensive discussion and analyses of these trends see the OTA report entitled *U.S. Dairy Industry at a Crossroad: Biotechnology and Policy Choices.*

Table 5-6—Summary Characteristics of Representative Moderate-Size and Large Dairy Farms, by Region

	Upper Midwest		Northeast		Southwest[a]		Southeast	
Characteristic	Moderate	Large	Moderate	Large	Moderate	Large	Moderate	Large
Cow numbers	52	125	52	200	350	1,500	200	1,500
Output/cow (pounds)	16,850	16,850	17,940	17,830	18,590	19,690	15,340	15,310
Total asset value ($000)	470	940	608	1,395	1,097	3,858	1,569	7,723
Land value ($000)	133	295	274	640	118	492	813	4,591
Percent of feed raised	63	60	50	46	0	0	25	2

[a]Includes farms from both the Pacific and Mountain USDA production regions

SOURCE: Office of Technology Assessment, 1992.

Table 5-7—Comparison of Average Annual Economic Payoffs From bST Adoption for Eight Representative Dairy Farms Under Three Alternative Dairy Policies, 1989-98[a]
(thousand $)

	Policyscenarios		
Region size	Trigger[b] price	Fixed[c] support	Quota[d]
Lake States:			
Moderate	**3.9**	4.1	2.4
Large	**10.3**	10.9	7.0
Northeast:			
Moderate	3.4	3.6	1.0
Large	15.8	16.6	8.8
Southwest:			
Moderate	26.5	26.6	18.3
Large	90.5	91.7	61.2
Southeast:			
Moderate	21.9	22.8	17.2
Large	166.4	166.3	132.0

[a]**Economlc payoffs from** bST are the average annual change **in net** cash farm income between a nonadopter and a bST adopter over the 1989 to 1998 planning horizon. The payoff is net of the cost of bST, the added transportation costs for milk, and the additional feed.
[b]This option triggers a price support reduction each time the level of government purchases of milk products exceeds 5.0 billion pounds annually.
[c]This option fixes the price support level at $10.60 per cwt. for all years.
[d]The quota policy is designed to maintain government purchases at or near a minimum government use target. This is accomplished by reducing the number of cows in a herd through a two-tiered pricing system or some other mechanism that provides disincentives for producing over quota levels.

SOURCE: Office of Technology Assessment, 1992

Swine Sector

As with the dairy industry, the swine sector will benefit from biotechnology improvements in the areas of reproduction, health, and growth promotants. Porcine somatotropin (pST), a growth promotant, will be one of the first technologies from the biotechnology era for the swine industry. Porcine somatotropin is a naturally occurring hormone in swine that accelerates the rate of growth, increases feed efficiency, and produces leaner hogs. Although the effects of pST on feeder hogs has **been known** for many years, it was not used commercially because of lack of availability. The ability to produce recombinant pST has heightened interest in using the product on commercial hog farms. Porcine somatotropin research has shown that it increases feed efficiency by as much as 40 percent, reduces fat by as much as 30 percent, and increases growth rate by as much as 33 percent. (See ch. 3.)

The economic benefits of pST can be discussed by analyzing representative hog producers in the Midwest who adopt pST, and the costs to producers who do not adopt pST. An economic model was used to simulate the economic viability of two Missouri grain-hog farms (75 and 225 sows) and two Indiana grain-hog farms (150 and 600 sows) before and after the introduction of pST. The Missouri and Indiana hog farms represent two different types of Midwest hog farms. The Missouri farms raise fewer pigs per sow, in part. because their operations are not total confinement operations like those representative of Indiana (table 5- 10). All the farms represent high-level management by progressive. full-time farmers intent on producing hogs efficiently with the best resources at their disposal. The farms were assumed to adopt pST on its introduction (1992) or not adopt it over the 6-year planning horizon (3).

Two pST/feed response scenarios were evaluated. The first represented the average gains from pST, i.e., 25.1-percent improvement in feed efficiency and a 12.7-percent increase in average daily gain. The second scenario assumed a more optimistic pST/feed response, a 34.8-percent improvement in feed efficiency and a 33.3 percent increase in average daily gain. In recognition of the reduced fat to lean reported for pST-treated hogs, a 5-percent price premium for market hogs was analyzed. This 5-percent carcass merit premium is within the range suggested in the literature.

Results of the analysis indicate that farms that do not adopt pST will experience lower annual net cash farm

Table 5-8—Impacts of bST Adoption on the Economic Viability of Moderate-Size Representative Farms, by Region, 1989-98 (in percent)[a]

	52-cow Upper Midwest		52-cow Northeast		350-COW Southwest		200-COW Southeast	
Measure of impact	Non-adopter	bST adopter	Non-adopter	bST adopter	Non-adopter	bST adopter	Non-adopter	bST adopter
Probability of survival[b] . . .	580/0	740/o	100"/0	100"/0	95%	97%	100"/0	1 000/0
Probability of earning 5-percent return on equity	58	74	100	100	95	97	100	100
Probability of increasing equity[c]	0	0	3	3	60	79	13	24
Present value of ending net worth as percent of beginning net worth[d] . .	16	29	72	77	109	128	76	89

[a]The analysis used a trigger-price dairy policy.
[b]Chance that the individual farm will remain solvent through 1998, i.e., maintain more than a 10-percent equity in the farm
[c]Chance that the individual farm WiII increase its net worth m real 1989 dollars through 1998.
[d]Present value of ending net worth divided by initial net worth indicates whether the farm increased (decreased) net worth in real dollars

SOURCE: Off Ice of Technology Assessment, 1992.

Table 5-9—impacts of bST Adoption on the Economic Viability of Large Representative Farms, by Region, 1989-98[a] (in percent)

	125-cow Upper Midwest		200-COW Northeast		1 ,500-COW Southwest		1 ,500-COW Southeast	
Measure of impact	Non-adopter	bST adopter	Non-adopter	bST adopter	Non-adopter	bST adopter	Non-adopter	bST adopter
Probability of survival[b] . . .	95°/0	99%	100"/0	100"/0	100"/0	100"/0	100"/0	100"/0
Probability of earning 5-percent return on equity	90	95	99	100	100	100	100	100
Probability of increasing equity[c]	8	12	43	53	100	100	88	99
Present value of ending net worth as percent of beginning net worth[d] .	57	69	92	102	195	214	129	147

[a]The analysis used a trigger-pnce dairy policy
[b]Chance that the individual farm will remain solvent through 1998, ie, maaintain more than a 10-percent equity in the farm.
[c]Chance that the farm WiII increase its net worth in real 1989 dollars through 1998.
[d]Present value of ending net worth divided by initial net worth indicates whether the farm increased (decreased) net worth in real dollars.

SOURCE: Office of Technology Assessment, 1992

incomes (ranging from $13 to $33 per sow) due to lower hog prices (table 5-1 l). (The lower hog prices are due to the increased supply of meat caused by the availability of pST.) This range of lost income is about the same across the four farms analyzed because it is a direct result of lower hog prices. For pST adopters this loss is more than offset by a 5-percent carcass merit premium for a leaner carcass. Increases range from $110 to $134 per sow (table 5-1 l).

Increasing the feed efficiency and average daily gain from pST to the more optimistic feed response scenario more than doubles the economic payoffs to adoption. Without the carcass merit premium, the economic payoffs for pST average $265 per sow per year, more than double the $100 spent for pST.[2] If the producers can garner a 5-percent carcass merit premium, the per sow returns to pST adoption to a total of about $370 per sow per year.

[2]The pST figure assumes that pST costs $6 per pig and is administered weekly for 6 weeks. The balance of the cost is added labor and feed costs.

Photo credit: Grant Heilman, Inc.

Production of lean meat with porcine somatotropin (pST) will give meat packers a strong incentive to vertically integrate or contract with farmers. Economic pressures will be strong for most swine producers to either adopt pST or to exit the industry.

The economic payoffs of pST adoption are about the same regardless of farm size. For example, the moderate-size Missouri farm's per-sow payoff is within 10 percent of that for the larger Indiana farm. And, the difference in payoffs between the 150-SOW Indiana farm and the 600-sow Indiana farm are within $18 per sow. These results suggest that pST could be scale neutral.

Nevertheless, pST could accelerate the concentration of the U.S. swine industry. PST adoption increases the total income of large-scale farms more than that of smaller scale farms due to the sheer volume of hogs produced on the large farms. For example, pST increases average annual net cash income $232,000 for the large Indiana farm and only $57.000 for the moderate-size Indiana farm. Thus, the large farm gains an internal source of capital for future growth far in excess of what the smaller farm gains. In addition, the smaller farms may experience lower average pST/feed response due to lower management skills while the larger farm experiences a higher than average pST/feed response and a 5-percent carcass merit premium. This results in the moderate farm's average annual returns to pST in the $3,300 to $18,500 per-year range while the large farm receives $232,000 or more per year.

PST may therefore contribute to a significant restructuring of the swine production sector. The production of more lean meat will give meat packers a strong incentive to vertically integrate or contract with producers and possibly pST suppliers. The economic pressures will be strong for most swine producers to either adopt this new technology once it becomes available or to exit the industry.

New Animal Products

Biotechnology methods capable of producing transgenic animals may alter the use of these animals from food to pharmaceuticals. Attempts are "being made to produce rare, medically important proteins in pigs. Production of blood-clotting factors and tissue plasminogen activator (used to dissolve blood clots that cause heart attacks) are being investigated. A private firm has announced that it has successfully produced human hemoglobin in pigs. A blood-clotting agent has been transferred to and expressed in sheep. Transgenic cows producing pharmaceuticals have not yet been reported, but these animals are under development in a number of public and private laboratories. If successful, the production of pharmaceuticals will open new markets for livestock. Incentives will be in place for pharmaceutical companies to vertically integrate or contract with farmers for the production of pharmaceuticals from livestock. Capital costs for breeding stock is most likely to be quite high indicating that successful, large farms are most likely to meet this new market demand.

IMPACT OF NEW TECHNOLOGIES ON AGRIBUSINESS, LABOR, AND RURAL COMMUNITIES

Agribusiness

Advancing products of biotechnology and information technology will have major impacts on agribusiness (input suppliers, processors, wholesalers, etc.). Historically. the commodity-oriented agribusiness sector has been driven by economic forces to produce at maximum efficiency and maintain low costs. This has resulted in a system that is remarkably effective at converting un-

Table 5-10—Characteristics of Representative Moderate and Large Grain-Hog Farms in Missouri and Indiana

	Missouri		Indiana	
	Moderate[a]	Large	Moderate	Large
Hog Enterprise				
sows	75	225	150	600
Boars	6	10	10	30
Gilts (repl.)	32	100	90	245
Pigs raised/sow/year	15.68	15.68	17.00	18.00
Gilts sold/year	556	,664	1,185	5,155
Borrows sold/year	588	,764	1,275	5,400
Sale weight	240	240	240	250
Lbs. feed/lb. gain	3.875	3.787	3.763	3.299
Assets ($1,000)				
Land	232.0	520.0	630.0	2,475.0
Buildings	70.0	175,0	120.0	500.0
Machinery	86.5	289.1	280.2	834.3
Livestock	34.4	65.7	49.9	158.6
Other Assets	0	0	0	0
Total	422.9	1,049.8	1,080.1	3,967.9
Liabilities ($l,OOO)[b]				
Real estate	30.2	69.5	75.0	297.5
Intermediate Assets	24.2	70.9	66.0	198.6
Other	20.8	54.8	70.6	40.6
Total	75.2	195.2	211.6	536.7
Net Worth ($l,OOO)	347.7	854.3	868.5	3,431.2
Acreage				
Owned	220	520	280	1,125
Leased	110	500	520	1,125
Total	330	1,020	800	2,250
Crops produced (acres)[c]				
Corn	144	300	540	1,800
Soybeans	80	333	175	400
Wheat	76	316	24	50

[a] The moderate size Missouri hog farm also has 25 cows on 100 acres of pasture.
[b] Liabilites are reported assuming the farm has 10-percent debt on real estate assets and 20-percent debt on machinery and livestock.
[c] Acreage of crops represents actual planted acreage in 1990 after accounting for set aside. All farms except the large Indiana farm participated in the farm program

SOURCE: Office of Technology Assessment 1992

differentiated commodities into relatively low cost food. Today this sector is undergoing change inspired in part by the evolution of a more demanding and differentiated food consumer. In response, retailer strategies have emerged which focus on improving service to the end consumer. Information technology has facilitated the shifting of marketing efforts toward the discovery of consumer preferences. Information technology along with legal disclosure requirements have made it easier for the consumer to see a wider range of product attributes. Where buying decisions were once made on such aspects as variety, convenience, price stability, and value, now consumers can also evaluate additional characteristics that were previously experienced only indirectly, such as product quality, nutrition, food safety, and environmental aspects (4).

To respond to a more consumer-oriented environment, input suppliers may need to explore how information technology can facilitate the coordination activities needed to assure particular attributes. In the future information technologies may facilitate new business strategies by providing improved information flows and by facilitating coordination of production and marketing activities. For example, Pioneer's *Better Life Grains* and Frito-Lay's *Frito Corn Chips are* two companies using information technology to assure product quality. Pioneer seeks suppliers who use a specific technology to tailor-make a seed that grows product specific attributes. Producers are required to provide specific production assurances that allow the processor to label the product for a specific set of nutritional attributes. Pioneer stands behind the attributes and accepts the implicit role as the enforcer, and information technology provides the linkages. Likewise, Frito-Lay contracts with producers for specific types of corn. The processed commodity is tracked through the market channel on a bag-by-bag basis to assure product quality (4).

Table 5-n—Average Annual Net Cash Farm Income Due to PST Adoption for Representative Missouri and Indiana Hog Farms Under Alternative PST/Feed Response and Carcass Merit Premium Assumptions

Representative farms	Do not adopt DST	Do adopt average pST/feed response		Do adopt optmistic pST/feed response	
		No CMP[a]	5 percent CMP	No CMP	5 percent CMP
	(thousand $)				
Missouri					
Moderate	56.73	57.70	64.98	75.59	83.19
Large	149.16	153.93	175.66	209.15	231.85
Indiana					
Moderate	214.22	217.53	232.66	255.48	271.70
Large	818.17	838.18	898.78	979.24	1,050.98
			$/sow		
Missouri					
Moderate	756	769	866	1,008	1,109
Large	663	684	781	930	1,030
Indiana					
Moderate	1,428	1,850	1,551	1,703	1,811
Large	1,364	1,397	1,498	1,632	1,752

[a]CMP refers to carcass merit premium.

SOURCE: Office of Technology Assessment, 1992.

Input suppliers have experienced more consequences of the biotechnology era than any other part of the agriculture industry to date. In anticipation of biotechnology-enhanced seed for large-acreage volume crops, seed and chemical input industries already have transformed structurally, just as the hybrid seed-corn industry developed to become a billion-dollar business after hybrid corn became a reality 50 years ago. With the expected future gains from biotechnology, multinational chemical and pharmaceutical companies have acquired almost all of the major seed companies. Only Pioneer Hi-Bred international and DeKalb remain independent firms (6).

Concentration of input industries increases the potential for monopoly power, hence the potential for exploiting farmers in their purchase of improved inputs. Overdependence on a narrow set of genetic material also raises the problem of ecological vulnerability.

Economies of size in process technologies also can foster concentration in the input sector. For example, a 7 million dose-per-day bST plant can supply two-thirds of the Nation's dairy herd. To the extent that efficient biotechnology manufacturing requires large plant sizes, there will be economic pressures to concentrate industry structure to a small number of firms. Moreover, in some cases, there may be incentives for manufacturing firms to integrate the manufacturing and retailing of inputs.

As discussed earlier. the trend toward vertical integration in agriculture and toward proprietary production processes could result in a captive market for some biotechnology products. For example, a genetically engineered seed might be produced by a large, vertically integrated chemical-seed company with specified inputs such as fertilizer, pesticides, and herbicides produced only by that company.

The potential for transgenic farm animals to produce pharmaceuticals will also provide incentives for vertically integrated companies. Firms already involved in pharmaceutical research can easily move into animal agricultural biotechnologies.

The increased importance of proprietary products and processes in the input-supply sector and the increased economic incentives for further industry concentration imply a challenge for small-scale firms. The survival of such firms may depend on public research in technologies that they can effectively use in their production systems; market access to these technologies; and easily acquired information on use and management of available technologies (5).

Farm Labor

As has been true for most past technologies, the emerging biological and information technologies will generally shift labor from farming. At the same time, new employment opportunities will be provided in the agribusiness sector supplying these new technologies. Today

Photo credit: Grant He//man, Inc.

Newly emerging technologies will displace less farm labor than mechinazation, but labor will have to be substantially more skilled than in the past.

only about 2 percent of the U.S. population is living on farms; about 55 percent of nonmetropolitan jobs in the food and fiber system are located off-the-farm in farm input, marketing, and other service sectors.

Newly emerging technologies will displace less farm labor than mechanization, but the farm labor force will have to be substantially more skilled than in the past. This will be particularly true for workers in animal agriculture. Demand for unskilled agricultural workers will fall off. Hired field workers will be limited to specialty crop (mainly fruit and vegetable) farms.

One message seems clear: implementation of the new technologies will require a broad range of specialized Skills. For example, a key requirement of the new information technology will be computer literacy. Enhanced management skills will be needed generally to succeed within a system characterized by increased technical and economic compltexity. Programs to support skill upgrading of the farm labor force will be needed to capture fully the potential benefits of new technologies (see ch. 6 for a more thorough discussion of these requirements.)

Rural Communities

The number of farms and farm population continued to decline in the 1970s and 1980s. The impacts of declining farm numbers are difficult to ascertain. In general, land is bought by other farmers and continues to remain in production so that total agricultural output does not significantly decline. However, declining farm numbers negatively affect rural community employment levels. In farming-dependent communities, for every one farmer that exits the industry, up to one additional job may be lost to the community.

While in most urban areas the 1980s were years of economic recovery and prosperity. this has not been the case for rural areas. The rural economic crisis was due in part to depressed conditions in export-dependent industries such as agriculture. forestry, and mining. However, even when these industries began to recover in the mid- 1980s, the rural-urban gap widened. This was due, in part, to the fact that rural problems run much deeper than those of agriculture alone. extending to inadequate infrastructure, poor schools. lack of access to quality medical services, and lack of leadership to solve problems that exist. While rural communities may have once been dependent on agriculture, only 23 percent of the 3,106 counties in (his country can now be described as agriculture-dependent, nonetheless, more than 75 percent of the Nations counties are nonmetropolitan. Rural communities and agriculture are no longer synonymous (1).

Much of the once agriculturally dependent popultition has moved to larger trade-center communities (many in nonmetropolitan counties), which have therefore grown in population and business volume. Growing communities in rural areas are often preferred locations for consolidated public schools, medical facilities. and other public services. Those communities left behind are suffering the consequences, and some are particularly vulnerable to the structure of agriculture.

The emergence of biotechnology and computer technologies will most likely spur on the decline of many small farms and agriculturally dependent rural communities. And, where product quality is influenced strongly by biotechnologies, such as pST in pork. and where highly specialized new markets are formed, such as pharmaceuticals, increased incentives for production-marketing links via contracting and other forms of vertical integration also can be expected. At the same time, increased demand by many farmers for one-stop shopping centers for farm supplies and technical services— including those involving biotechnologies and computer

Photo credit: Grant Heilman, Inc.

Advancing technologies will most likely spur on the decline of agriculturally dependent rural communities. These business communities will need to substitute additional nonfarm economic activities if they are to remain viable.

technologies—may reduce the viability of business enterprises in smaller rural communities. These business communities will need to substitute additional nonfarm economic activities if they are to remain economically viable (5).

In the near term, biotechnology's effects on rural communities likely will be most significant in regions of concentrated livestock production. The ability of rural communities in these regions to absorb adverse changes in agricultural employment will be closely related to the availability of off-farm employment.

Because rural communities have diversified their economic base and are no longer dependent on agriculture, most rural community residents have little or no personal contact with farming, except as passive observers of environmental changes. The environmental impacts of production practices can, however, become a community issue when such externalities as water quality, chemical residues, worker safety, etc., become sources of concern. Local sensitivities about the implications of novel substances employed in animal and crop production already are significant. Perceptions of risk to health, safety, and/or environmental diversity associated with transgenic organisms may become a further source of community conflict and controversy.

To ameliorate such conflict and controversy, communities should facilitate:

1. open public discussion of biotechnology research priorities;
2. enlightened policies and procedures regarding approval, patenting and regulation of biotechnology innovations; and
3. insistence on high-quality and timely information about biotechnology for public and private decisionmakers.

POLICY ISSUES

A number of policy issues surround the introduction of technological innovations in U.S. agriculture and their impacts on the industry. Many are already on the policy agenda in one form or another. Several are discussed below.

Moratoriums on Agricultural Research or on the Implementation of New Agricultural Technology

Moratoriums have already been placed on the use of bovine somatotropin in Minnesota and Wisconsin. The dairy case study discussed earlier clearly showed that regardless of farm size or region, there will be strong incentives to adopt bST. The farms in Minnesota and Wisconsin, even if they do adopt this new technology, still will have problems realizing sufficient earnings to achieve a reasonable return on equity, compete, and survive. For farms not adopting the new technology the dilemma will be even more severe. The agricultural industry of these States will be at a great disadvantage relative to those States where a moratorium does not exist if bST is approved by FDA for commercial use.

In the process of economic development a maturation process occurs such that fewer human resources are required in primary industries (farming and mining) and proportionately more workers are employed in the knowledge and service industries. American agriculture has achieved its preeminence in the world by substituting knowledge for resources. This knowledge, embodied in more productive biological, chemical, and mechanical technologies and in the managerial skills of farm operators, has given the United States a world-class agricultural industry at a time when many other sectors of our economy are losing their preeminent position. For U.S. agriculture to retain its status it is necessary to enhance public and private-sector capacity for scientific research and technology development. The costs, to consumers and producers, of failure to maintain and enhance our

efficiency in production would greatly exceed the adjustment costs resulting from overabundance.

Impacts of Emerging Technologies on Farm Size and Managerial Skill Requirements

The post World War 11 era of farm mechanization made it virtually impossible for small unmechanized production units to compete and survive with farming as the sole source of family income. Some past chemical and biological technologies such as insecticides and hybrid seed, on the other hand, have been rather scale neutral except for price discounts afforded producers who were able to purchase them in large volume. The emerging biotechnology and information industries appear to have the potential for being relatively scale neutral in their application on those *farms already large enough to support mechanization technology.* **But two qualifying considerations are important.** First, the implementation of these emerging technologies will generally require increased management skills and, for some, computer literacy. Second, at least some of these technologies will be effective and profitable only if they are integrated into rather technically complex production systems at the farm level. Some of these systems in animal agriculture may involve environmentally controlled housing and scientifically based feeding and management procedures. Thus, increased managerial skills, and, in some cases, additional capital in the form of specialized buildings and equipment will be important components of successful farming in the future. This will most likely mean increased concentration of farm production among larger units with more sophisticated technology and management capabilities.

A number of persons who have moved out of farming in the past four decades did have adequate skill levels but had an inadequate resource base of land or operating capital to succeed under a highly mechanical farming regime. Future adjustments in farming will be dictated less by large capital requirements than by the educational and managerial skill requirements for farmers. This is not to suggest that the future capital requirements in farming will not be high. They will. In fact, the capital requirements per worker in farming are very high compared to most other types of employment. But recent major deflation in agricultural capital assets, particularly farm real estate, together with creative procedures by farmers for acquiring access to land and capital resources, may result in educational and managerial skill levels becoming a more limited resource than capital. One clear-cut conclusion emerges. Persons who want to compete successfully in farming will need to upgrade their managerial skills. A critical role for Extension is to develop programs and opportunities for farmers to enhance their management capabilities.

Displaced Farm Operators and Workers

More workers have left farming since 1940 than now remain on U.S. farms. Displacement of farmers and farm workers will continue, though at a slower pace than in the past half century.

Adjustment to alternative employment is most easily accomplished by young people who are just graduating from high schools, vocational schools, and colleges or universities. Thus. strong educational programs and vocational counseling for youth in farming communities are of vital importance. Selected public policies should aim at ensuring the provision of such educational support services. Other displaced farm workers will seek nonfarm employment either with or without retraining for such employment. A number of special training programs are already in place for such individuals. These retraining programs. however, need to be geographically and financially accessible and have appropriate entrance requirements for those displaced from farming. Moreover. they need to target employment training to those skill areas for which jobs are available.

A number of older farm operators and other family members without new training may have to adjust to whatever full- or part-time employment opportunities exist in the local community. The availability of such employment opportunities and the general quality of life in many rural farm-dependent communities will be heavily dependent on the local farm economy. And, in some cases businesses based on newly emerging technologies, particularly those supplying farm inputs, will provide new local employment opportunities.

Adjusting to Change

Policies to help farmers adjust to technological change on the farm or to off-farm employment are lacking. The Food, Agriculture, Conservation, and Trade Act of 1990 and related farm policies are aimed almost exclusively at reducing the use of farm inputs (mainly land) to curtail farm output; providing a price (and income) floor for producers of selected commodities; and enhancing the position of U.S. farm commodities in world trade. A unique exception was the dairy herd buyout program in the late 1980s, which provided some dairy farmers with an opportunity to “cash out” their dairy herds at more attractive prices than those afforded by the free market. New or expanded public policies are needed for upgrading the managerial skill levels of some farmers to cope with technical

change and for providing retraining opportunities for others to enable them to exit from farming. Strong educational programs are also needed for all rural young people whether or not they have opportunities in future ''high-tech' farming. Expanded Federal and State assistance will be required for effective educational programming in those rural areas with an eroding local tax base.

At the institutional level, public institutions need to aim policies and programs at two somewhat different types of participants—those who will adjust by staying in farming, and those who will seek alternative employment. Both groups need to be serviced by effective public technology transfer and training programs and supporting financial services. A reorganized and revitalized public extension service could play a major role in technology transfer while public credit agencies need to focus program delivery on the special needs of the two target groups. At the farmer level, it is crucial that individuals realistically assess their opportunities in and out of agriculture. Most should make deliberate career choices and follow up with the acquisition of the managerial skills to succeed in high-tech farming or the retraining required for employment off-the-farm. Future farm commodity programs are not likely to provide an umbrella of income protection adequate for any but those farm managers who can adjust effectively and quickly to technological change.

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Chapter 6

Management Implications of New Technologies

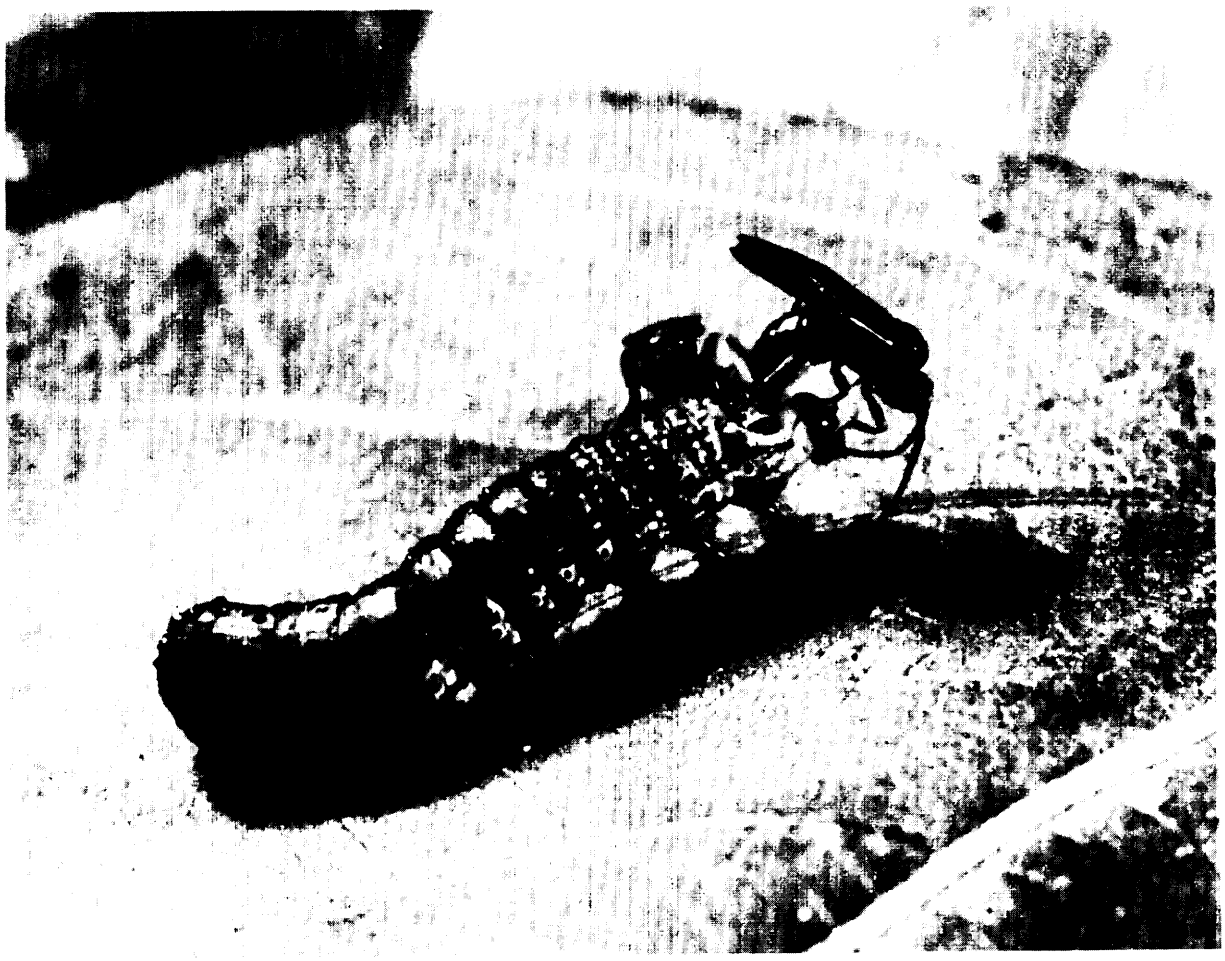

Photo credit: U.S. Department of Agriculture, **Agricultural Research Service**

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Chapter 6
Management Implications of New Technologies

Biotechnology holds great promise for American agriculture, but this promise may not be realized if the technologies are poorly managed. The new technologies will demand considerable management skills and a holistic or systems approach to management. Pest resistance to technologies that control pests exemplifies management problems in the past. Many chemical pesticides are ineffective today because of pest adaptation. Evidence suggests that pest adaptation could have been delayed and, in some cases, avoided if proper management strategies had been implemented. As products from the biotechnology era are used to control pests, management strategies for delaying or possibly avoiding pest adaptation need to be identified.

Good management will be of paramount importance for the effective use of new biotechnologies in animal agriculture. The new technologies are not magic bullets, and will not improve animal productivity without effective management. With or without biotechnology, a growing management issue in this decade is farm animal well-being. Little scientific evidence is available on farm animal well-being in the United States; much more is available in Europe. It is important that the American animal agricultural industries begin to focus more attention and resources on this growing issue and on the impact of new technologies on farm animal well-being.

This chapter focuses on these critical management issues. First, pest adaptation to various control technologies is explored for crop agriculture. **Various management strategies** for delaying pest adaptation are identified for the new technologies developed through biotechnology. Second, the importance of the farm animal well-being is discussed, areas of research are identified, and biotechnology's potential impacts on farm animal well-being are explored.

INTEGRATED PEST MANAGEMENT STRATEGIES FOR CROP AGRICULTURE

Pest infestation is a serious problem for agriculture and effective methods to control pests are needed. Of all crop pests, weeds boast the longest recorded history of adapting to agricultural practices. It is a history dotted with examples of one of nature's most interesting adaptive strategies: mimicry (35). By mimicing crop seed, weed seeds can lie hidden among crop seed stored for the next season's planting.

Successful mimicry of agricultural crops requires that weeds possess a number of important characteristics. Weed seeds must ripen by harvest time; remain on their stems during harvesting; and have a shape and density similar to that of the crop seed (35).

A surprising number of weeds have evolved all the characteristics required to become crop-seed mimics. An example comes from the mimicry of lentil seeds, Lens *culinuaris,* by the common vetch, *Vicia sativa.* The lentil seed has a convex shape. Normal seeds of the common vetch are much more rounded than lentil seeds (figure 6-1). Another example is one of rice's most serious rivals, barnyard grass. Barrett (1) discovered in weedy forms of barnyard grass so many rice-like traits that they found it more difficult to differentiate barnyard grass from rice than to distinguish two variants of barnyard grass from each other (figure 6-2).

In the mechanized farming systems dominant in the United States, hand weeding may be a thing of the past, but the battle between farmers and weeds continues. Chemical herbicides used to control weeds do not discriminate on the basis of appearance. The nature of the game has switched to biochemical mimicry. Agricultural chemical companies spend millions of dollars each year inventing chemical agents that kill weeds in cultivated fields without harming crops. This has put enormous selection pressure on weeds to biochemically mimic crops. It is estimated that there are at least 84 cases of weeds with resistance to at least one chemical herbicide (figure 6-3).

Like weed resistance to herbicides, the resistance of plant-pathogenic fungi to synthetic fungicides is a significant problem. By the mid- 1980s, more than 100 species were known to be resistant to at least one fungicide (figure 6-3). [1]

The real experts at resistance to synthetic chemical agents are insects. Resistance to DDT, detected shortly after its introduction as one of the first insecticides, is

[1] On the **other hand,** some pesticides have **remained** effective over the **long term. For** example, glyphosate has been used to control weeds for more that **17 years without** any documented examples of **resistance.** Likewise there is no evidence **of** codling **moths (pests of apples) developing** resistance to organophosphates even **though** these **pesticides** were used intensely for 20 years to **control the moth (34).**

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frequently cited as a textbook case of rapid adaptation. Since DDT, insects have been most successful at adapting to almost all insecticides. More than 500 cases of insect adaptation to insecticides have been documented (figure 6-3).

Besides the growing problem of pest resistance to chemicals, there is much criticism of chemical pesticides because of their adverse environmental side effects (95). "Natural" control methods are often touted as safe and effective alternatives to chemical pesticides, but there is no guarantee that pests will not adapt to these methods as well. Indeed, numerous examples abound of pests overcoming a wide variety of control methods. Pests have adapted to cultivation methods as illustrated by wild vetch in lentils and barnyard grass in rice (34). Pests also have adapted to crops bred to be pest-resistant. For example, a random sample of 63 plants bred for resistance to viral pests indicated that pests had adapted in 28 cases. Only five cases showed no evidence of viral adaptation, and the rest were inconclusive (20). Insects also have adapted to crops bred for insect resistance. Hessian flies in wheat, green bugs in grain crops. and leafhoppers and planthoppers in rice are examples (22, 33). Other insects have adapted to biological control agents. For example, alfalfa weevils and the forest pest *Pristophora erichsonii* have adapted to parasitic enemies, and silkworms have adapted to fungal control methods (34). Some strains of insects, the diamond back moth, for example, have developed resistance to biological control with *Bacillus thuringiensis (56, 80, 91),* a bacterium that is toxic to many insect pests.

These examples lead to three basic conclusions:

1. pests have demonstrated tremendous ability to adapt to almost any control mechanism,
2. unilateral pest suppression tactics rapidly can be rendered ineffective due to evolutionary change in pests, and
3. the assumption that natural pest control tactics are superior to synthetic methods, at least in terms of limiting pest adaptation, is false.

Control of pests requires the use of many approaches, rather than reliance on one single method. A holistic program that considers all causes of plant stress—pathogens, weeds, insects and other arthropods, water and nutrient excesses and deficiencies, soil pH, salinity etc., is needed. However. developing such an integrated approach will require an enormous amount of information and an understanding of the interactions among different stress-reduction strategies. Much effort will also be needed to educate farmers in taking such a multifaceted approach to pest and other stress control.

Figure 6-l—Successful Seed Mimicry by Common Vetch Weed of Lentil

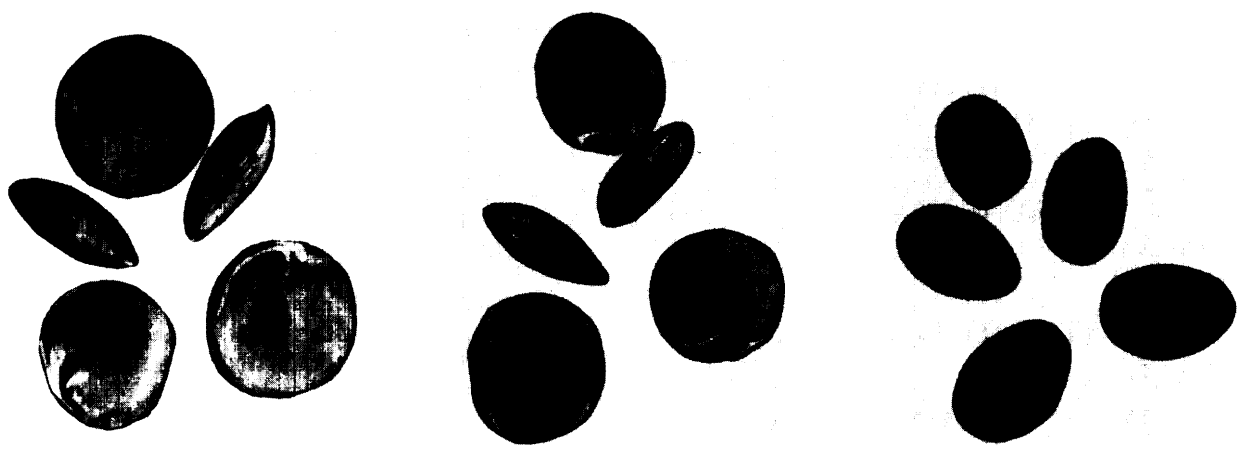


Photo credit: Virge Kask

Success at seed mimicry has given the common vetch the ability to contaminate lentil fields. At left is the typical seed shape of the common vetch, *Vicia sativa.* In a lentil field near Albion, Washington, plant pathologists recently found vetch seeds that had a distinctly different shape (center) that is quite similar to the flatter shape of the lentil, Les*culinaris* (right).

SOURCE: Richard M. Hannon, U.S. Department of Agriculture, Agricultural Research Service

Figure 6-2-Successful Mimicry of Barnyard-Grass Seedling for Cultivated-Rice Seedling

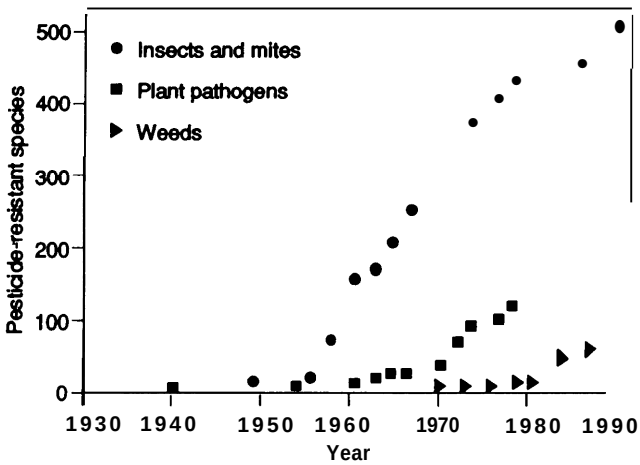
Photo credit: Beverly Benner

Survival in a hand-weeded field is easier for a weed that looks like a crop plant. A barnyard-grass seedling, a serious nuisance in rice fields, is easily mistaken for a cultivated-rice seedling. Left to right, the plants shown are cultivated rice, the ***oryzicola*** variety of barnyard grass, and another barnyard grass seedling.

SOURCE: Spencer C H Barrett, University of Toronto

Integrated Pest Management (1PM) represents an attempt at such an approach. 1PM strategies seek to create a crop management system that combines compatible production techniques and methods in a manner that maintains pest populations at levels below those causing economic crop injury. The 1PM approach is based on ecological principles and requires a solid understanding of the ecological system to be managed. Development and deployment of integrated strategies requires basic knowledge about target pest species and their interactions with other pest and beneficial species, as well as with the crops to be protected and other host plants (70). Knowledge of the direct and indirect effects of other crop production and protection inputs on nontarget pests and beneficial species is also essential. Because crop/pest interactions display tremendous geographical variation for the same crop and pest, pest management systems must be adapted to local conditions. The complexity of, and lack of adequate knowledge about, pest populations and agroecosystem dynamics make 1PM an unrealistic goal at this time.

Figure 6-3—Number of Crop-Pest Species Resistant to Synthetic Chemical Pesticides.



SOURCE: N.G Green, H.M. Lebaron, and WK. Moberg, Managing Resistance to Agrochemicals: From Fundamental Research to Practical Strategies (Washington, DC: American Chemical Society, 1990).

Limited 1PM strategies have been used in cotton and apples to control insects, rather than weeds or disease (2 I). Presently, 1PM efforts focus on integrating cultural controls (sanitation, crop rotation, appropriate selection of planting dates, irrigation regimes, planting densities, varietal selection); naturally occurring biological control; and the application of chemical controls when pest populations or damage to the crop reaches a threatening level. These action thresholds are based on the complex and dynamic relationship between crops and pests throughout a growing season (72).

Combinations of pest-control methods ideally should act synergistically to control pests; at least they should not counteract each other. Research shows that synergism exists between some moderately resistant plants and biological control agents; in other cases, such plants adversely affect the activities of naturally occurring biological control agents (32).

Compatibility with biological control agents must be a significant consideration when biotechnology is used to create resistant crop varieties and to extend the range of biological control agents. Some preliminary research involving tobacco that has been genetically engineered to produce low levels of *Bacillus thuringiensis* (Bt), indicates that Bt does not negatively affect natural enemies of tobacco budworm. It is possible that Bt enhances the effectiveness of the natural enemy by slowing budworm growth (34).

Crops that have low to moderate levels of pest resistance, generally have responded well to chemical controls. Several cases have been documented where pest suppression has improved following insecticide use on resistant crop varieties (48, 93). However, there are also examples of antagonistic interactions (53, 55).

Crop rotation has been employed effectively to decrease pest infestation. However, continuous cropping has also lead to a decline in incidence and severity of pest infestation by providing a more stable environment for the establishment of naturally occurring antagonistic agents. For example, the severity of take-all disease in wheat has naturally declined in fields that have been continuously planted to wheat for years. The decline is due to the establishment of a bacterium that controls the disease (97). Little is known about the compatibility of genetically engineered crops and cultural practices. Currently the use of constitutive genes (i. e., genes that are expressed in all tissues at all times in the plant) leave little room for temporal flexibility.

In the above examples, the compatibility of only two control mechanisms for one pest is considered. However, many other plants, animals, and microbes, some of which are beneficial and some harmful to crops, are also part of the agroecosystem. Most of these components are studied in isolation; in a truly integrated system, all control mechanisms used to control all pests should be compatible. For example, mite management of almonds cannot be discussed without considering how simultaneously to manage codling moth, navel orangeworm, and weeds (49, 101, 102). The information needed to do this currently is unavailable.

As practiced currently, 1PM strategies do not eliminate but strive to decrease chemical use by improving the timing of pesticide application to achieve pest suppression with minimal nontarget effects. Improved pesticide application technologies to minimize off-target drift could also decrease amounts of pesticides used. Pesticide delivery equipment designed to directly mix pesticides at the proper rate, eliminating the need for tank mixing, could increase the efficiency of pesticide application (78, 95).

Development of pest management technologies and programs does not automatically lead to their adoption. Many obstacles stand in the way of farmer acceptance of these programs. The complexity of the programs requires high levels of management skill and this is a significant deterrent to many farmers. Information and programs tailored to meet the local needs, perceptions, resources, constraints, and objectives of farmers is imperative. Many farmers will need considerable training to use these technologies. The lack of coordination among organizations, personnel. and disciplines involved in pest management at the local and regional levels inhibits educational efforts. Development of expert systems and other information technologies may help in training and in coordinating these efforts (see ch. 4) (34).

The failure of growers to perceive the long-term cost advantage of integrated pest management strategies is a significant deterrent to adoption. There is a general need to demonstrate how these management strategies might reduce production costs. For example, almond producers were generally skeptical of adopting an integrated mite management program, until it was shown that this program could be effective, was compatible with pest control tactics already being used, and could result in decreased production costs of $24 to $44 per acre (47). Developers of pest management technologies generally lack the social science training needed to demonstrate cost-effectiveness to farmers. Input from social scientists is needed to successfully develop and implement any new methods.

Management of pests will continue to be a major concern of agricultural producers. Successful development and adoption of more comprehensive pest management strategies will require extensive scientific research, as well as improved methods of providing readily usable information to agricultural producers. A better understanding of the interactions between crops and pests and of mechanisms of resistance development is needed. Changes in farm management practices also may be needed. The ongoing battle to stay one step ahead of pests, given their ability to adapt, will require the development of new biological control agents, improved chemical pesticides and wholly new technologies such as genetically engineered plants.

Biotechnology holds great promise for providing new ways to control plant diseases, insects, and weeds. The tools of biotechnology have created the possibility of selectively engineering plants for insect, disease, and weed resistance. In addition, these new tools are expanding the knowledge base of plant resistance and the interaction of plants and pests with the rest of the ecosystem. In particular, biotechnology will be very useful in detecting resistance by pests at a much earlier time than traditional technologies and in developing strategies to slow or alleviate pest resistance.

Molecular Genetics as a Tool for Detecting Resistance and Tracing its Origins

Until recently, pesticide resistance could be detected only after it became a problem in the field or through laboratory bioassays in which samples from a pest population are treated with predetermined doses of the pes-

ticide in question. The number of samples that can be processed in this fashion is low, especially with insects and some weeds.

If an enzyme that leads to resistance has been identified. another approach to detecting resistance is development of monoclinal or polyclonal antibodies to that enzyme (see ch. 3 for explanation of how they work). Although there are certain drawbacks to this approach, there is a potential with this system to detect resistance at very low levels using kits that can be applied directly in the field.

With many pests, resistance develops in a number of localized geographic areas. It often is not clear whether these localized resistant populations arise independently or whether one population becomes resistant and rare migrants invade new areas and become the dominant form in the newly invaded area. It is important to know which of these two scenarios reflects the dynamics of resistance in order to limit further progression of the resistance problem.

If the resistance developed in one location and spread to another via migration, then the mutation(s) leading to resistance are probably rare. It may be advisable to attempt to quarantine the areas of resistance and to eradicate pests within these areas. On the other hand, if resistance arises independently in each area. then the mutation frequency is probably high and the above strategy would be useless. If the biological mechanisms of resistance in two areas are clearly different. it is safe to assume that resistance arose independently. However, when the mechanisms of resistance are similar it is possible that resistance had one origin.

Advances in molecular genetics have allowed scientists to clone the genes responsible for some kinds of pesticide resistance. By determining the point at which a mutation in the gene occurred in a number of different populations it will be possible to more precisely determine the number of origins of resistance. Work in this field is only beginning but progress in at least one case has been astonishing. A French molecular biology group working with a Culex mosquito species was able to demonstrate that a single, initial, mutation in an esterase locus (an enzyme that accelerates the synthesis of esters) is responsible for most of the organophosphate resistance in this species worldwide (76). Their molecular analysis demonstrated that the DNA sequences adjacent to the coding region of the gene were identical in all resistant populations.

The Influence of Genetically Engineered Crops on Pest Resistance

Two primary questions arise about pesticide resistant crops (and about herbicide tolerance in particular): whether the level and pattern of pesticide use will be altered by such crops; and/or whether crop production patterns will be changed. Impacts that might occur as a result of these changing patterns also need to be evaluated. Impacts include environmental and food and water safety issues and continuing or increased problems with resistance. No definitive data exists on these issues, only reasonable speculation on changing patterns (but not levels) of herbicide use that might occur. There is also reasonable speculation about changing crop patterns and pesticide use that might result from insect and disease resistance. However, more data is needed to assess environmental and food safety issues. Speculations about changing crop patterns combined with knowledge of how pest resistance develops does lead to some conclusions about the type of resistance problems that might arise. It also suggests some farm and industry management strategies that might be pursued to minimize resistance. These issues are discussed below (34).

Herbicide-Tolerant Crops and Weed Resistance to Herbicides

Today agriculture depends to a great extent on herbicides to control weeds. Herbicide use patterns (and related pest-resistance problems) are affected by many factors, including price, the spectrum of weeds controlled. residue effects, flexibility or timing of pre or postemergence treatments, marketing strategies, and ease of use. While biotechnology may contribute to pest resistance risks in some cropping situations, it is only one of the factors involved, and its application to American agriculture must be considered holistically.

Biotechnology-agrichernical companies. and seed companies as well as public universities and laboratories are using genetic engineering to develop crops resistant to herbicides. With herbicide-tolerant crops greater quantities of particular herbicides can be used to control weeds. As the name implies, herbicide-tolerant plants can grow in the presence of herbicides that harm or kill a nontolerant plant. Some plants naturally tolerate particular herbicides. Grasses, for example, naturally tolerate certain herbicides that kill broad-leaved plants. Despite this, use of herbicides to control agricultural weeds is often limited by the sensitivity of a cultivated crop to a herbicide or by the sensitivity of other crops that subsequently will

be planted in the same field. Herbicide-tolerant crops remove this limitation. They are designed to tolerate higher levels or more potent doses of herbicides than non-tolerant crops. A concern is that herbicide-resistance weeds may be created by the transfer of herbicide-tolerance genes to weedy relatives of crop plants or by the change in patterns or levels of herbicide use. Herbicide-tolerant crops could lead to increased problems with weed resistance or diminish these problems depending on the types of herbicide-tolerant crops developed and the manner in which they are deployed (27, 28). We must proceed with caution in developing and deploying herbicide tolerant crops.

Resistance of weeds to herbicides is a recent problem that is predicted to worsen during the next decade. As herbicide use increases (a possible consequence of herbicide-tolerant crops) so does selection pressure for resistant weeds. Furthermore, gene mutation leading to resistance to some of the newer herbicides occurs at a reasonably high rate, leaving these herbicides in a vulnerable position.

Research has shown that a number of the new herbicides (e. g., sulfonylureas, imidazilinones, and triazolopyrimidines) have the same target site in the plant, the ALS enzyme (acetolactate synthase), which is essential for plant growth. These herbicides bind to a nonactive site of the ALS enzyme, change its confirmation, and thereby inactivate it. Resistance to herbicides that inhibit the ALS enzymes has been found in eight weed species, and primarily arises through a change in the nonactive site of the enzyme (57). The mutation rate for this change is quite high (1 in 1 million) and companies are well aware that this presents a problem. Adaptation of a weed to one herbicide moreover can render the weed resistant to a number of other herbicides, a phenomenon called cross resistance (75). Overuse of a single ALS inhibiting herbicide or a group of ALS inhibitors in one area thus could be problematic.

For example, continuous use of ALS inhibitors in soybeans and corn maybe ill advised in that it may accelerate development of resistance in target weeds. In 1991, two new herbicidal products, both ALS inhibitors, were labeled for use in corn. If these are used on a substantial crop area and other ALS inhibitors are also used on soybeans in the same area, risk of weed resistance will be significantly increased. Because the spectrum of weeds that a given herbicidal product can control is limited, a single product is rarely used everywhere or all the time. The higher the diversity of ALS inhibiting compounds, the greater the acreage that is likely to be treated with an ALS inhibitor.

Herbicide Use in Corn/Soybean Rotations—Many herbicides fall into two groups based on their spectrum of activity: broad-leaf herbicides; and grass herbicides. This dichotomy presents a short-term agricultural problem. Broad-leaf herbicides can be used in corn (which is a grass), but could be a problem in soybeans since it is a dicot (i. e., broad-leafed plant). Conversely, a number of herbicides that can be used in soybeans could be damaging to corn (e. g., Scepter).

Until this year, imidazilinone and sulfonyl urea herbicides were used only in the soybean component of corn/soybean rotations. Care had to be taken so that residues would not carry over to and damage the next year's corn crop.

Recently, collaborative work between American Cyanamid and Pioneer has lead to development of corn with tolerance of the imidazilinone products, Scepter and Pursuit, both ALS inhibitors. Scepter is currently used in southern areas on the soybean component of soybean/corn rotations and Pursuit is used similarly in more northernly areas. If corn cultivars with imidazilinone resistance were introduced to areas with corn/soybean rotations, the door would be opened for the use of more ALS inhibitors in these areas. Pioneer is currently planning to release imidazilinone-resistant corn cultivars in the early 1990s in areas that do not generally use soybean/corn rotations (17). Since these areas grow continuous corn this could mean continuous use of these ALS inhibitors. Such an introduction must therefore be considered carefully. If tolerant corn cultivars were also released in areas with soybean/corn rotations, more land would receive continuous control with ALS inhibitors.

Biotechnology could, on the other hand, be used to diminish risks of herbicide resistance in weeds. The ALS inhibitors are being relied on increasingly as they replace older herbicides with known environmental problems or high costs. Other types of herbicides are available that affect different target sites in weeds (e. g., glyphosate, glufosinate). Some of these compounds are limited in use because specific crops lack tolerance to them. If, for example, corn cultivars were developed with glufosinate or glyphosate tolerance, it might allow farmers to alternate use of ALS inhibitors and compounds with a different mode of action.

Monsanto is currently trying to develop soybeans with tolerance to glyphosate based herbicides (e.g., Roundup). If they are successful and such soybeans were introduced

Photo credit: Grant Heilman, Inc.

Research is ongoing to develop soybeans with tolerance to glyphosate based herbicides. if successful, the cycle of continuous use of ALS inhibitors could be broken, thus slowing the development of resistance to target weeds.

into corn/soybean rotations, the cycle of continuous use of ALS inhibitors could be broken.

Herbicide Use in Cotton—Although cotton is sometimes rotated with other crops such as soybeans and corn, in major cotton producing areas of Louisiana. Mississippi, and Arkansas 75 to 80 percent of the cotton lands are planted to cotton for 5 or more years in a row (6). While soybean and cotton may be grown on the same farms, the land with the highest yield potential generally is reserved for cotton. Only about 5 percent of the land in these areas is rotated between cotton and soybean.

Currently, mid-south cotton generally receives three herbicide applications, one pre-emergence and two post-emergence. The most commonly used post-emergence treatments involve mixtures of Monosodium Methane Arsenate (MSMA) and fluometuron (a substituted urea) for the first post-emergence treatment, and Disodium Methane Arsenate (DMSA) plus cyanazine or prometryn (triazine compounds) as the second treatment. To date, none of these has caused significant resistance in weeds or environmental problems (7), although DSMA- and MSMA-resistant cocklebur has been found in North and South Carolina (58). Some of the major weeds requiring control are the morningglories, cocklebur, prickly sida, and sicklepod, but the weed complex varies geographically, and from farm to farm.

At least two companies have been working on developing transgenic cotton with herbicide tolerance. Calgene has had success in engineering cotton with tolerance of bromoxynil (a benzonitrile compound), which controls broadleaf weeds (87). Bromoxynil is especially effective against lambsquarters and young morningglories but is less effective on some other weeds.

Monsanto has been attempting to develop cotton with tolerance to glyphosate. The company seems to have had some success but has altered its strategy because the original approach was not leading to sufficient tolerance levels. Monsanto has isolated what it considers promising genes to insert into cotton but has not yet tested them in any plants.

Even if a high-yielding cultivar of bromoxynil-tolerant cotton were readily available, it is not clear how much acreage would be treated. Bromoxynil has a limited spectrum of activity and it will probably be heavily used only when lambsquarters or morningglory is the dominant problem. Where lambsquarters is the major problem, bromoxynil could be used twice a year. Where morningglory is the problem, bromoxynil will probably only be used once, in a post-emergence spray since other compounds can be used more effectively later in the season.

Adding bromoxynil to the cotton system could result in use of more diverse classes of herbicides (and mechanisms of weed toxicity) than are currently used in that system. Little concern exists that bromoxynil will decrease this diversity (7). Thus, transgenic cotton with Bromoxynil resistance is unlikely to present a problem in terms of fostering weed resistance.

If Monsanto succeeds in producing cotton with glyphosate tolerance, a very different situation may arise in cotton. Glyphosate is an effective broad-spectrum herbicide that can kill broad leaf weeds as well as grasses. If cotton were tolerant of glyphosate, this compound could replace the current post-emergence herbicides in a large portion of the cotton growing areas. While current post-emergence herbicides are generally effective, they could not match glyphosate for effectiveness nor for ease of use. Monsanto feels that two applications of glyphosate could replace current post-emergence combinations (14). Monsanto plans to lower the price of glyphosate to make it competitive with current practices (14). The U.S. use patent on glyphosate has been extended until the year 2000, but outside the United States this patent will expire soon if it has not already (26). A company in Canada is already gearing up to man-

Photo credit: Grant Heilman, Inc.

Scientists have had success in engineering cotton with tolerance to bromoxynil which controls broadleaf weeds. Adding bromoxynil to the cotton system could result in use of more diverse classes of herbicides and thus it is not likely to foster weed resistance.

ufacture a glyphosate-based herbicide. These changes offer incentives to reduce the price of the compound to gain market share. This price reduction would tend to make the compound appealing to farmers.

The potential, thus, exists for glyphosate to be used over a large area, two or more times each season. If this happens will there be a high risk of weed resistance developing'? Given the information we have to date there is no simple answer to this question. Box 6-A contains a review of some points made by scientists involved in the ongoing debate about this issue.

Most of the crops that have been targeted for herbicide tolerance research are large-herbicide-use crops (i.e., the money makers). Perhaps a more important need is for herbicide tolerance in limited acreage crops for which there are few herbicides available. Herbicide tolerance could open the door for use of safer herbicides in these crops. Additionally, with limited acreage crops the risk of weeds evolving herbicide resistance is probably lower than with major crops.

Crop-to-Weed GeneTransfer— Before the biotechnology era, resistance of weeds to herbicides evolved through mutations in the weed plant's own genetic material. The possibility that herbicide tolerance genes, engineered into crops, could find their way into weedy relatives of the crop has recently received considerable attention (e.g., Bioscience, June 1990).

What will be the fate of such transferred genes, and will they increase the risk of herbicide tolerance evolving in weeds? There is no answer to these questions yet but some general statements can be made. First, it is generally assumed that natural rates of mutation leading to resistant traits in weeds are one in a million or less. Thus, any introgression (the entry of a gene from one gene complex to another) between the crop and an important weed that increases this rate without lowering the fitness of the weed could be of importance.

If genes that reduce the fitness in the hybrid are tightly linked to the herbicide tolerant gene(s), the latter might not remain in the weed population long enough to cause a problem. Only empirical studies will determine the likelihood that a herbicide tolerance gene would free itself from fitness-reducing, or ''encumbering' genes and become a problem.

There are at least three things that could be done by genetic engineers to lower the risk of herbicide tolerance genes finding their way from crops to weeds, and leading to resistant weed strains. First, when developing transgenic crops containing the herbicide tolerance gene, molecular geneticists could determine if certain inserts map closely with specific crop traits that would tend to lower fitness of a weed. Second, when developing the initial constructs, a second gene could be inserted that would serve as a suicide gene if expressed in a weed seed (i. e., it would kill the whole weed).

A final strategy would involve engineering herbicide tolerance into plants that required two genes to be effective. If the two genes were placed on separate chromosomes the chance that both genes would segregate when they were at low frequency in the weed population would be minuscule in an outcrossing hybrid. This could dramatically slow the rate of increase in frequency of the tolerance trait. A similar result could be achieved if the tolerance trait was controlled by a single recessive gene.

Crops With Resistance to Pathogens

The only breakthroughs in genetic engineering that are likely to affect pathogen control practices in the near future involve virus resistance. Work on engineering plants to express viral coat protein genes and antisense genes has resulted in plants with significant protection against

Box 6-A—Glyphosate: A *Risk to Weed Resistance?*

History

Glyphosate hadbeen in widespread use for at least 17 years and no cases of resistance have been documented that could be directly traced to its use. However, due to its broad spectrum of activity, glyphosate has not been used on crop fields except in cases where weeds need to be controlled in fallow rotations. Most of the weeds that it has been used to control are perennials, and these weeds are less likely than annuals to evolve rapidly resistance. In at least one situation, however, glyphosphate has been used to control annual grasses in fallow rotations every other year for a long period of time with no sign of resistance. it has also been used on orchards **(14).**

Chemistry

Although glyphosate rapidly is degraded by some soil bacteria, plants apparently lack enzymes that can degrade this compound. in screening for resistance to glyphosate, Monsanto scientists have never found a plant enzyme that could degrade glyphosate. This further suggests that weeds are unlikely to mutate such that they become resistant to glyphosate (35).

Mode **of** Action

Unlike the sulfonyl ureas and imidazilinone herbicides that bind to an inactive site of a critical plant enzyme, glyphosate binds to the active site of an essential enzyme for synthesis of certain amino acids. Crop tolerance could be engineered by interfering with glyphosphate binding to this site. Any alteration in the active site that would inhibit glyphosate binding, however, potentially could also impair the binding of the enzyme to its target molecule and diminish the fitness of the plant. Monsanto's experience indicates that this is indeed the case. This has apparently been one of the factors that has made it difficult for them to engineer crops with glyphosate tolerance. While overproduction of a less efficient form of the enzyme is possible, it still could lead to decreased growth efficiency.

Lack of Persistence

One important characteristic of glyphosate is that it does not persist in the environment. Therefore, weed control exerted by this compound is restricted to those weeds that are actually sprayed.

Concision

Certainly the question of potential of weeds to adapt to glyphosate is not yet resolved. However, it seems clear that glyphosate poses less risk than some of the ALS inhibitors. The information to date would suggest proceeding with caution in developing and deploying glyphosate-tolerant cotton.

SOURCE: Office of Technology Assessment, 1992.

a number of viruses (2). Such plants could be used widely in developed and developing countries. They certainly have the potential to raise yields. The question is whether this increase of yield will be stable.

For 28 of 63 traditionally bred virus resistant crops examined, virus strains have been positively identified that could overcome the resistance (20). In only four cases was there good evidence that there had been no adaptation. Results were equivocal for the remaining cases. It is not clear whether or not we should expect the same track record from crops with genetically engineered resistance.

Only one short-term experiment attempted to look for genetic adaptation to engineered resistance. This experiment was reported on in an anecdotal fashion (2). He indicated that he had propagated a TMV virus to high levels in an attempt to induce systemic infection of resistant plants. He passed the virus through the resistant plant seven times, after which it was collected and tested for rate of disease development. This rate was unchanged.

This experiment was obviously a good first step in evaluating the potential of a virus to adapt to engineered resistance. Studies using a broader base of viral isolates and conducted over a longer period of time would be advisable and very useful before any engineered germplasm is relied on to increase yields in developing countries.

Engineered Plants With Insect Resistance

Background—There has been a great deal of interest on the part of industry in developing plants with resistance to insects. Although most of the traditionally-bred, resistant crop cultivars owe their resistance to secondary plant compounds (e.g., alkaloids, phenolics, terpenes) and changes in physical characteristics (e.g., spines, waxy leaves, solid stems) these traits are generally controlled by many genes and are not amenable to straightforward engineering approaches.

Molecular geneticists have instead taken the approach of 1) finding a protein from a bacterium, plant, or an animal that is toxic to insects (e. g., venoms, bacterial toxins), 2) finding the gene that codes directly for the protein, and 3) inserting that gene into a plant. Sometimes this approach works well as with the crystal protein toxins from *Bacillus thuringiensis* (Bt) (59). In other cases, this approach is only partially successful, probably because the proteins are digested in the insect gut before they reach their site of action. If it were simple to design toxic proteins that could withstand the gut enzymes, plants would probably do so themselves. Another successful approach to engineering insect resistance involves the proteinase inhibitors, whose site of action is the insect gut itself. Unfortunately, high levels of the proteinase inhibitors are usually needed to inhibit insect growth.

Of all the potential approaches to engineering insect resistant crops, those involving the Bt crystal proteins are farthest along. Crops that have been successfully engineered to produce insect-toxic proteins include tobacco, tomato, cotton, and potato. Other crops targeted for Bt crystal protein production include but are not limited to corn, rice, soybean, cucumber, and eggplant.

The mother bacteria for the Bt toxin has been used for many years as a biological insecticide by organic farmers and to a limited extent by others. Recently, there has been an increase in the use of these bacteria in conventional, production agriculture. This is in part due to increased pest resistance to conventional pesticides. For example, few insecticides are still effective against diamondback moth and the Colorado potato beetle (23). Other reasons for increased use of *Bacillus thuringiensis* include better formulations and increased toxicity. Both conventional breeding and genetic engineering have been used to improve the potency of the bacterium. The Mycogen company in California has taken the gene from a crystal protein and placed it in another bacterium. They have reported field results indicating that their product has slower decay in the field than normal Bt strains and therefore is more useful for the farmer (23). Ecogen, a company in Pennsylvania, has ‘‘bred’ a strain of Bt that produces two crystal proteins, one effective against lepidoptera (caterpillars), the other effective against beetle larvae. This product offers useful control of the Colorado potato beetle and the European corn borer when they infest potato.

There appear to be some good markets for Bt products, whether engineered in plants or used as biological insecticides. One very good thing about using Bt is that it is not likely to disrupt natural enemies of pests or hymenopteran pollinators found in the crop, because most natural enemies and bees are immune to the effects of Bt. This property should make the use of Bt or Bt genes compatible with biological control.

Again, the major question is whether or not Bt will offer long-term solutions to pest problems or whether pest insects will adapt to Bts and nullify their utility. There has been much concern over this issue. In the mid 1980s, there was a feeling among some workers that insects would not adapt to Bt (8). Many early attempts to select for resistance failed or produced very low levels of tolerance (24). In 1985, however, McGaughey (65) found that Indian meal moths selected in the laboratory for Bt resistance became over 100-fold resistant.[2] Further work by McGaughey and his colleague led to a level of resistance in excess of 250 fold. McGaughey and Johnson (66) also found cross-resistance to a number of other Bt strains. This was considered by some scientists to be an exception, but in 1989 Monsanto scientists published work (89) indicating 20 fold resistance to a Bt toxin in one member of the cotton bollworm complex, a major target for Bt toxin production. Further work by the Monsanto group found up to 70 fold resistance of cotton bollworms to this toxin (60). Ongoing research has found resistance in this insect to a number of Bt toxins, to plants expressing the toxin, and to mixtures of Bt spores and crystals (36).

However, all of the above work was done in the laboratory, and field results do not always match laboratory findings. Nonetheless, in 1988 there was a report of field failure of Bt sprays in the Philippines due to resistance

[2] The meaning of this term involves a ratio. For example, if it takes 200 micrograms to kill a resistant pest compared to 2 micrograms to kill a susceptible pest, the pest has a 100-fold resistance (200 divided by 2).

Photo credit: Monsanto Co.

The large boll of cotton on the left is the product of a transgenic plant with Bt genes. The boll on the right was grown in the same field but comes from an unprotected, nontransgenic plant. However, resistance to Bt by bollworms is a very real possibility.

of the diamondback moth (56). in 1990 resistance was carefully documented in a crop field in Hawaii (9 1). The level of resistance in Hawaii was about 30 fold. Recent evidence of Bt resistance in Florida, Southeast Asia and Japan indicate levels as high as 400 fold in the diamondback moth (85). There is no longer any doubt that at least some insects are very capable of adapting to Bt and Bt toxins.

Recent work on the biochemistry of resistant Indian meal moths indicates that the difference between susceptible and resistant individuals involves a change in a receptor binding site in the midgut of the caterpillars. Interestingly, a change in the receptor that leads to resistance to one Bt toxin does not necessarily lead to resistance to other Bt toxins (96). For some insects (e. g., diamondback moth. cabbage worms), scientists have found two or more distinct groups of toxins with high activity. For species like the cotton bollworm. only one group of toxins offers high activity.

There is high risk of resistance to Bt in some cropping situations. If a crop or a set of crops is engineered to produce a Bt toxin and is planted widely, the potential for resistance must be considered.

Cotton—One of the first major crops in which Bt genes may be commercialized is cotton. Monsanto claims to have Bt toxin expression high enough to kill 100 percent of the insects placed on a cotton sample in the laboratory. Close to that level of success was achieved in the field. Monsanto intends to commercialize Bt-producing cotton in the early-to-mid 1990s.

In some areas of cotton production, cotton and soybeans are grown on the same farms although not rotated on the same field. This could be helpful in limiting selection pressure on bollworms to adapt to Bt-producing cotton because some of the insects (a refuge sub-population) will feed on soybeans. The effects of insects in refuges has been described earlier and can be quite important, especially if adaptive genes are recessive. Unfortunately, large tracts of cotton acreage are planted in solid blocks. Potential for resistance in these areas will be quite high. As long as the size of the bollworm populations is large there is likely to be sufficient genetic variation to lead to resistance. While it is impossible to say for sure that the bollworms will be able to adapt to Bt in the field, laboratory results certainly support this possibility.

Potato—Two types of Bt-toxin genes have been engineered into potato. Plant Genetic Systems in Belgium has engineered a Bt toxin into potato that is active against the potato tuberworm. Monsanto has engineered a beetle-specific Bt toxin into potato and reports to have achieved high levels of Colorado potato beetle mortality.

The Colorado potato beetle (CPB) is notorious for adapting to pesticides. One reason for this is that there are few refuges for this beetle. When potatoes have been heavily sprayed with insecticides. it has very few alternative plants on which to feed.

However, there is only one report of CPB resistance to Bt. which comes from a laboratory study in Michigan (68). Results of this study were only briefly described but seem to indicate approximately 30-fold resistance. No field resistance has been reported. It is difficult to assess the meaning of this since Bt sprays capable of controlling CPB have only recently come to market and have not been used widely.

If potato plants with Bt expression are introduced and used widely, the selection pressure for potato beetle adaptation is likely to be as strong as that exerted by insecticides.

Corn—Success with transgenic corn is very recent. Therefore, it is too early to know just what levels of Bt toxin expression will be obtainable in this crop. There is no doubt, however, that one of the goals of molecular **geneticists** in industry is development of corn with Bt toxin levels high enough to control European cornborer.

The European cornborer currently causes over 10 percent yield reduction in certain areas of the United States (54) but is rarely the target of chemical control measures. In general, chemical control is not economically profit-

Photo credit: Grant Heilman, Inc.

Molecular geneticists have had recent success in developing transgenic corn with Bt levels sufficiently high to control the European cornborer. In the corn belt, there would be few alternatives for cornborers so Bt resistance could be strong, especially if corn is planted in monoculture.

able because of the low value of the crop (on an acreage basis) and the difficulty of controlling this insect because of its habit of feeding in crevices and within plant tissue. Bt expression in corn would be a very desirable trait from the perspective of yield. If some farmers start to use it early on, they will have at least a temporary yield advantage over their neighbors. Certain areas of the United States where cornborers cause more yield loss than in other areas would gain an advantage. This would occur because their yield increase would be greater than in other areas (54).

It is possible that corn seed with Bt genes would be adopted widely if it were priced low enough. In the corn belt there would be few refuges for the cornborers, so selection pressure for Bt resistant strains would be strong. In other areas of the country where corn is not planted in huge monoculture and cornborers feed on other crops (e.g., potato, beans, cotton, peppers, etc.), selection pressure would not be as intense.

Strategies for Delaying Pest Adaptation

Need for a Comprehensive Approach—From the farmer's perspective, the history of pest control is the saga of a long struggle to stay a step ahead of pest adaptation. Some of the techniques used to combat pests have proved relatively resistance-proof, **but these successes** have been limited (34). The experience with synthetic chemical pesticides has been particularly disappointing.

There is growing recognition among scientists that they need to maintain an arsenal of pest-control tools in anticipation of pests' evolutionary responses. That arsenal contains some potentially powerful weapons, among them the novel approaches of biotechnology.

Much of the discussion of resistance management for at least the past decade has centered on ways to reduce the rate at which pests adapt to conventional pesticides. Yet pests adapt not only to pesticides but also to other agricultural pressures, and they interact with other parts of the environment in important ways.

Thus, management strategies must take into account the entire spectrum of pest adaptation. As discussed above, insect adaptation to Bt toxin genes is a problem today. The following discussion of management strategies to delay insect adaptation to Bt is an example of a comprehensive approach that needs to be implemented generically for pest resistance in general.

Case Example—Adaptation to Bt—There exist six basic strategies for delaying insect adaptation to plants expressing Bt toxin genes (31), each of which is appropriate in a different crop/pest system. The basic strategies are:

1. high expression of a Bt toxin gene with no refuges,
2. high expression of a Bt toxin gene with refuges,
3. high expression of two or more unrelated toxin genes with refuges,
4. low expression of a toxin gene to slow the growth and vigor of the pest to complement natural enemies of the pest,
5. expression of toxin genes only at times and in plant parts where protection from pest damage is required, and
6. restricting Bt use to minor crops.

These strategies for delaying adaptation to Bt are based on the same general principles of population genetics that apply to resistance to conventional pesticides. The important differences between strategies for delaying resistance to Bt toxins produced by plants, and to mechanically applied pesticides derive from inherent differences in these two toxin delivery systems.

The mechanical delivery systems for insecticides usually have considerable temporal flexibility. When a scout determines that the number of insect pests in a crop is

reaching an economic threshold, the information can be relayed to the farmer or crop consultant who can make the decision to spray the field with the appropriate insecticide. The farmer or consultant may have a number of insecticides on hand to choose from or can purchase them quickly. The insecticide can be applied to the field within hours if weather is not a problem and equipment and labor are available. Even in problematic cases, the insecticide can generally be applied within a few days. While there is some spatial flexibility in mechanical application procedures, it is generally not feasible only, for example, to spray plants that have two or more insects cm them.

Mechanical application also permits flexibility in dosage applied. Dosage can easily be adjusted to field conditions and to the species and developmental stage of pest requiring control. The only lack of flexibility is in cost: the more you apply, the more it costs. Given insecticide decay rates in the field. doses will decrease after application and must be renewed at a cost. if needed.

When the plant's genetic system is used as the delivery system the situation is different. The genomes of plants and other organisms are set up to turn genes on and off as they are needed to produce specific proteins. It would not be useful for a plant to turn on a gene in a root cell if that gene was involved in producing the red pigment for flower petals. A lot of work has been conducted by molecular biologists' to learn how genes are turned on and off. An important component of these switches resides in DNA sequences that flank the sequences that actually code for protein production.

Some flanking sequences cause a gene to be expressed everywhere continuously; others turn the gene on only in certain plant parts; still others activate the gene only when the plant experiences a specific type of stress such as drought or attack by insects. Comments from industry (37) indicate that the first set of engineered plants to be commercialized will express Bt toxins by relying on "constitutive" promotors, that is, flanking sequences that activate genes under almost all conditions. This means that there will be little temporal flexibility regarding when and where a toxin is produced.

In contrast to traditional pesticides, which can be applied as soon as reports of insect abundance warrant, seeds with the Bt genes must be purchased weeks or months before planting. Thus, a farmer has to assess how intense pest problems will be before a crop is even in the ground. If there is even a small chance of a pest problem and Bt seed is not too expensive, the choice will not be too hard unless the farmer has an individual concern about resistant pests. Use of Bt plants thus is generally referred to as prophylactic pest control as opposed to responsive pest control where toxins are only delivered when a problem is detected.

Another difference between transgenic plants and conventional insecticide-based control programs is that the dose of a conventional pesticide can be adjusted based on need; with engineered plants the "dose" of Bt delivered is predetermined. Once the seed is in the field there is no flexibility.

However, there is room for spatial flexibility in the use of engineered Bt plants. One option that a farmer has with cultivars that produce Bt continuously is to mix seed from the Bt cultivar with that of a closely related cultivar that is not resistant to pests (Strategy 1 and 2). Under certain conditions such a mixture would inhibit a pest outbreak without producing strong selection for Bt resistance. A number of models have been developed to look at this resistance management strategy, and results indicate that resistance does develop more slowly, especially if the Bt genes are recessive (29, 30).

As indicated above, a number of forms of Bt toxins affect different insects. In cases where two or more distinct types of Bt toxin are available for use on one pest it is possible to have both expressed in the transgenic plant (Strategy 3). Theoretical models indicate that planting seed with two or more dissimilar toxins along with 20 to 50 percent seed that was entirely susceptible to the insect pest could preserve crop resistance 20 times longer than use of the single toxin strategy in some crop/pest systems (29, 30).

There has been a good deal of work done on how "partial" plant resistance to insect pests could "work with' natural enemies of the insect pest to deter an outbreak (Strategy 4) (38). Scientists have conducted field tests with engineered tobacco that produces a low level of Bt toxin that causes about 15 percent mortality of larvae and slows the growth of survivors. The Bt was found to have no negative effect on the natural enemies of the budworm and may indeed lead to more natural enemy-induced mortality of young budworms than would otherwise be the case. This may be the result of larvae growing slower or being more restless on the plant.

This low dose strategy may be a good one in some cases but not in others. Two problems that can arise are 1) natural enemies that cause indirect selection for adaptation to the Bt, and 2) pest genes that mediate adaptation to mild (not high) Bt stress. This later problem is considered important in the medical field where it is

sometimes advised that if antibiotics are used they should be used at high levels (9, 44, 73). Rigorous testing of the basis for this advice seems to be lacking.

As indicated earlier, some genes in plants are only activated in certain plant parts at certain times (Strategy 5). Molecular geneticists have been able to move the gene activity promotors from one organism to another and basically get the same pattern of gene activation. For example a promotor region from soybeans that turns on a gene only if it is in the developing seed's cells was moved to tobacco and only turned on the gene in the tobacco's developing seed (3). Promotor sequences from tomato that only turn on adjacent genes when there is pathogen or insect stress have also been moved to tobacco and operate just as they did in the tomato (82).

In some crops only certain plant parts need protection from insect damage. For example, the buds of the tobacco plant must be protected against the tobacco budworm but this insect also feeds on leaves. If the buds were protected, the budworm might switch to feeding more on mature leaves. Studies indicate that the budworm is expected to develop Bt resistance more slowly if only some plant parts express the Bt genes (36).

In some crops the plants only need to be protected at certain times of the season (e. g., cotton). If Bt toxin genes were only turned on at specific times in the plants' developmental cycle, the insect would experience selection pressure in one instead of three generations a year. This also should slow the development of Bt resistance.

Since some plant genes are turned on only when there is **tissue damage,** it may be possible to find promotors that would operate like an automatic pest scout and turn on Bt genes only when a threshold of damage had occurred. Such a system would turn engineered plants from a prophylactic pest control tool into a responsive pest management tool. Such a change could significantly reduce selection for Bt resistance, especially with pests that only reach outbreak numbers once every few years.

As with engineering crops for herbicide tolerance, much of the work to develop insect-resistant transgenic plants has focused on the major cash crops. This makes sense because potential industry profits are higher from working with these crops than with minor crops. If profit were not the major concern, other issues might dominate the decisions about which crops to engineer. For example, pesticides protect many small-acreage vegetable crops from insect pests up to harvest. Pesticide residues in fruits are a concern. If Bt is indeed harmless to mammals it would be useful to replace the chemical pesticides with Bt. In many cases only a small percentage of an insect pest population feeds on these minor crops, so selection for resistance to Bt would be much lower than it is in cotton or corn. If use of Bt was restricted to such crops, it would be possible to achieve long-term environmentally sound pest control (Strategy 6).

Weediness of Crops With Pest Resistance

Most traditional crops such as corn and tobacco are unlikely to start reproducing like weeds (i. e., uncontrollably) solely because they have pest resistance. However, semi-domesticated crops are another matter. Poplars, pine trees, and many pasture grasses and legumes can already compete well in natural habitats. Pests help maintain a balance among plant species in a pasture or forest. In mixed hardwood/pine forests, insects and pathogens are important sources of tree mortality. If a gene for insect or pathogen resistance were placed in a stand of cultured pine trees, and pollen from these trees were to reach native pines there could be a problem. Or if pine trees became resistant to their insect or microbial pests but the hardwoods did not, it is reasonable to expect a significant shift in the balance of hardwoods to pines in forest. The practical and aesthetic impact of such a change in forests must be considered.

POLICY IMPLICATIONS REGARDING THE DEVELOPMENT AND DEPLOYMENT OF ENGINEERED CROPS

If we maintain a laissez-faire policy regarding pest control, it is likely that developed products will be those expected to sell best. For example. farmers who have not been specifically educated about Bt-producing plants are unlikely to buy seed that produces moderately resistant plants (with hopes that natural enemies can control the rest) if seed selling on the same shelf for an equivalent or lower price produce highly resistant plants.

Only if companies exert restraint in marketing their seed will there be any potential for a multifaceted approach to resistance management. For example, if only one company has a product (such as Bt in cotton) priced such that only 50 percent of the farmers in an area decide to use it, other approaches will be adopted. When two companies have the product this is less likely to happen. Even when one company controls the market, economic analyses may dictate going for the highest volume of sales.

In that Bt is a naturally occurring organism that has been used by organic farmers for many years, there may be potential for regulating the use of Bt products based on resistance risk, even though synthetic chemicals have not been regulated on that basis. If it can be shown that the traditional uses of Bt would not lead to evolution of resistance as rapidly as new biotechnology approaches using Bt toxins, there may be grounds for some regulation of use. This issue is not yet resolved and the Environmental Protection Agency (EPA) does not seem to be pursuing the issue.

Weed resistance problems may be somewhat different than insect resistance problems. In the case of most insects, resistance is an area-wide phenomenon—what one farmer does affects other farmers in the region. The stage is set for a tragedy of the commons with no farmer willing to comply with practices that would help others who may be cheating. Weed seed and pollen do not move as far as most insects, so resistance can become a single-farm or even a single-field phenomenon. If one farmer overuses a herbicide and winds up with a resistance problem, other farmers who hear about it may be cautious about using that herbicide too frequently, even if it is inexpensive. If glyphosate use leads to resistance in one area of the mid-south, farmers in other areas may respond by becoming more cautious in decisions to use the product. Educational programs to point out risks to farmers would be very appropriate, and could be very effective in this case, but much research is needed to bolster the information content of such educational programs.

Overall, we already have enough information to formulate general policies that prescribe judicious use of engineered crops with insect and pathogen resistance and herbicide tolerance. However, if we are to make detailed rulings about the development and use of specific products of biotechnology, we will need to generate a body of empirical knowledge relevant to these products. And, we will need an educational program designed to bring these results to the farmer and the public.

A NEW ISSUE IN ANIMAL AGRICULTURE MANAGEMENT

The use of new animal technologies will place a premium on the management capabilities of livestock producers. Research results clearly show the extent of response achieved depends heavily on the management capability of the producer. Use of somatotropins, for example, may require altering the animals' diets. Growing pigs receiving somatotropin will require diets high in protein, and with adequate levels of the necessary amino acid, lysine. Administration of somatotropin to lactating cows may require extending the reproductive cycle to 14 months instead of using the current 12-month cycle. The availability of many different types of growth promotants may result in the use of more than one at the same time. Compatibility of these promotants will be an important management issue. Thus, producer management skills are critical to the optimal use of these technologies.

As important as these management issues are, a more pressing management issue is that of animal welfare—with or without biotechnology as a complicating factor. Society has focused on many of the resulting impacts of technologies such as environmental quality, food safety, and decline of the small farm and rural communities. Farm animal well-being is the most recent concern to receive attention. Much of the success in increased productivity in agriculture has been the result of lowered costs through the use of confinement systems—which some have coined factory farming. The question from an animal welfare perspective is whether we have gone too far.

Farm Animal Well-Being

In the decade of the nineties, the advance of new animal technologies will coincide with increasing interest in farm animal well-being. This interest is not new. It nucleated in England at the turn of the 19th Century with the formation of the Royal Society for the Prevention of Cruelty to Animals. This in turn led to the organizing of more radical groups. In America, the American Society for the Prevention of Cruelty to Animals was formed in the 1860s by a Special Act of the New York State Legislature. However, it was not until the late 1970s and early 1980s that the majority of animal welfare/rights organizations were formed. Although no specific records are kept, estimates indicate that today there are a total of 7,000 animal welfare/rights groups in the United States with a combined total budget of $50 million (81).

Widespread public concern for farm animals began to develop in 1963 with the publication of *Animal Machines.* This book by Ruth Harrison (46) chronicled the problems in farm animal well-being in the United Kingdom that led to the Brambell commission and its report enunciating the famous ''Five Freedoms' '—to lie down. stand up, turn around, stretch, and groom.

Concern built steadily in Europe, and in 1979 the first European meeting on farm animal welfare was held. European governments have allocated significant public funds to research on alternative farm systems and the European

Community (EC) has supported numerous symposia on the well-being of various farm animals. Legal protection for farm animals includes far-reaching laws in Sweden and Switzerland.

In the United States the level of concern has grown more slowly. However, in the past few years the pressure on farmers and animal scientists to address the issue of farm animal welfare has increased steadily. The issue of farm animal welfare has provided important impetus to a movement that may eventually be considered as significant by policy makers as that for environmental and food safety concerns. Today, the issues of animal welfare/rights foster well-entrenched polar positions. The polarity between the agricultural establishment and animal well-being advocates has highlighted the extremes of each group's position. Economics, values, and institutions determine care and treatment of farm animals. These factors divide into two animal welfare paradigms: the traditional and the alternative. Which paradigm will dominate future public policy for animal welfare remains to be seen (94).

The Traditional Paradigm

Those who hold the traditional paradigm of animal welfare draw on the market model of free enterprise, and on Judeo-Christian ethics.

The Market Model—Advocates of the market model argue that farm animals subject to cruelty and neglect give fewer eggs and less milk, meat, or wool than well-treated and properly cared for animals. Why not, they ask, depend on profits to ensure farm animal welfare?

Quantifiable variables such as feeding efficiency, rate of growth or productivity, morbidity, and mortality rates can provide proxy measures of animal welfare. Favorable values for those objective measures of humane treatment for the most part are consistent with good management and high profits.

Advocates of the market model further argue that confinement systems improve some dimensions of animal welfare. Temperature, disease, and pest control are improved. Predators are kept away. Nutrition is enhanced. Modern farming systems have lowered costs and expanded utilization, allowing more animals to exist.

The Judeo-Christian Ethic—Advocates of the traditional paradigm hold the Judeo-Christian ethic that God created man in his own image, that man is **unique in** having a soul, that man has dominion over animals, and that man as husbandman and steward of God's kingdom is not to practice cruelty to or neglect animals (77, 86). Many advocates of this position hold that no element of society has more compassion for poultry and livestock than does the farmer (45). Other than laws protecting animals from cruelty and neglect, advocates of this view consider laws, rules, and regulation on care and treatment of farm animals to be unwarranted infringement on free enterprise. This creed holds that 1) proprietors deserve the right to prescribe rules under which they operate; and 2) a prime function of government is to prevent anyone, including the government, from infringing on the managerial freedom of proprietors (5).

Some traditionalists will admit that, despite market incentives, cruelty-neglect laws, and producers with the Judeo-Christian ethic, animal welfare falls short of the ideal. But they contend that ''Big Brother' intrusions of an expensive and often incompetent bureaucracy into managerial prerogatives of farmers would entail more social cost than the abuses government is attempting to correct. They favor minimal policy intervention consistent with the traditional paradigm as the lesser of two evils.

Alternative Paradigm

An increasing number of people reject the Judeo-Christian ethic and market paradigm in favor of an alternative paradigm emphasizing animal rights or much enhanced animal welfare. As with the traditional paradigm, the alternative has economic and ethical dimensions.

Market Failure—Animal welfare has public goods properties, implying that the market alone will not bring the proper level of animal welfare. Externalities are apparent: all the public benefits from seeing livestock freely grazing in a meadow. Animal rights activists contend that the market results in confinement cages allowing too little space per animal for laying hens, sows, and veal calves. The drive to reduce costs and cater to consumer demand has kept veal calves isolated, in the dark, and on low iron diets; has disfigured animals, by encouraging practices such as trimming chickens' combs and beaks and pigs' and lambs' tails. According to activists, animals are not allowed their "natures' '—socialization, sex, exercise, nest building, nurturing of offspring, the outdoors, and a full life.

However. the role of markets in shaping the way farm animals are raised cannot be denied. Market forces have raised real prices of land and labor, and reduced the relative price of capital. Rising labor and land prices have placed a premium on labor-saving and land-saving meth-

ods of production. Gains in income and population along with changes in production technologies, including disease control, have interacted with prices to create economies of size and to make confinement systems feasible. Small may be beautiful but it is frequently not competitive. The small-scale poultry operator is nearly extinct; the small Wisconsin dairy has difficulty competing with the large industrial-type California dairy farm; and the family hog farm in Iowa has difficulty competing with the large confinement operations in Arkansas. Animal welfare enthusiasts view these outcomes of market forces as a disaster to farm livestock and to traditional farmers, rather than as a means toward cheaper food. more land for urban use, and higher income for the Nation.

Ethics—The alternative paradigm views man as an evolutionary product of a holistic Nature. Man is one with nature and must live in harmony with plants and animals. If he has primacy, it is to be used to ensure the rights of the rest of nature.

Philosopher Jeremy Bentham's (4) much-quoted comment summarizes the basis for the ethical treatment of animals under the alternative paradigm: ''The question is not Can they reason'? nor, Can they talk'? but, Can they suffer'?'

Animals that are sentient (can experience pleasure or pain) are to be afforded rights given to people. Killing an animal is murder and eating its flesh is cannibalism. Hard-core animal rights adherents have little alternative to vegetarianism. Other advocates do not go that far but insist on improving animal welfare through provision for each species' nature.

Animal suffering and pain is probably the most powerful rationale for the public's concern over farm animal welfare. This concern must be addressed by objective research.

Research Needed

To understand and fulfill agricultural animals' needs, more must be learned about their fundamental psychological and behavioral processes. Researchers must be able to elucidate farm animals' cognitive and motivational processes before it is possible to begin to answer such rudimentary and obvious questions about their well-being such as: How does this animal feel in one environment versus another? Is the animal suffering—and if so. how much? For example, when the animal's farm environment is devoid of a particular feature that would characterize its natural environment, does the animal suffer—and if so, how much (11, 12)?

The scientific community generally has been slow to accept the notion of animal awareness and only recently has such recognition been forthcoming. Many in agriculture now acknowledge that animals are aware of themselves and their surroundings, and thus scientists are beginning to give attention to animals' conscious sensations of well-being. Only recently have factors that affect conscious well-being been considered logical criteria for the design of animal accommodations. However, there exists little hard data on which to base such a design strategy.

How an animal feels, some assume, depends largely on how it expects to feel. How it expects to feel in turn depends on how it thinks, remembers, and imagines. How an animal feels also depends on factors such as the predictability and controllability of its environment (100).

Feeling, thinking, remembering, and imagining are cognitive processes. To the extent that feeling and thus, thinking, remembering, and imagining affect an animal's overall well-being, and therefore its health and productivity, these cognitive processes are factors to be considered in the economic and humane production of agricultural animals.

There is reason to believe that when an animal experiences a feeling of malaise, its productivity is reduced, if only slightly. However, such decrements are cumulative; and together they can reduce productivity significantly. In the chicken, for example, there is recent evidence that as many as six stressors—ammonia, beak trimming, coccidiosis, electric shock, heat, and noise—can combine in additive fashion to affect feed intake, growth, and several important physiological and pathological traits (64). In addition, stressors and combinations of stressors occurring in various sequences affect productive performance of chickens in predictable, repeatable ways (52). This linear additivity of stressor effects on such a variety of traits suggests that some single phenomenon is governing the animals' overall response. This could be psychological stress. The following discussion depicts some of the production practices that animals encounter and areas of research that are needed (12).

Thermal Comfort— Little is known about the perception of thermal comfort by farm animals (10). Animals do respond to changing conditions in their thermal environment with different thermoregulatory **behaviors. But** the degree to which animals suffer when experiencing heat stress or cold stress is not known. One experiment to find the answer to cold stress of farm animals is cur-

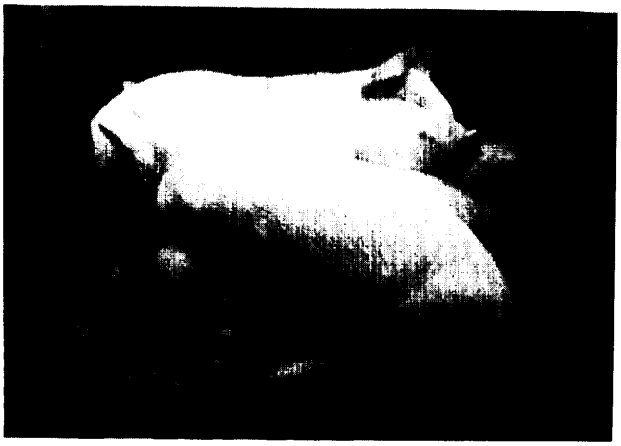


Photo credit: University of Illinois

An example of a thermal comfort experiment involving pigs operating a heat switch. The sitting pig—presumably because it felt the environment was too cool—has just operated the switch in the panel to engage the heater.

rently underway involving pigs operating a heat switch when they feel cold.

Another thermoregulatory behavior response is wallowing by swine under heat stress. Wallowing in mud compensates for the pig's absence of thermal sweating. Research has shown that sows wallow only when environmental temperature exceeds some threshold (e.g., 12 "C for sows in one experiment) (83). This limited research suggests that swine wallow only to achieve thermal comfort, not because they need to wallow or enjoy wallowing as play. If the thermal environment is maintained below 12 "C all the time, sows never take advantage of a mud wallow even if it is provided.

Quality of Space-The richness of an environment is somehow perceived by animals because it affects how they behave and function. The behavior repertory of swine in natural settings is larger than it is in typical production environments (88).

When contemporary production environments are furnished with enriching features, pigs readily make use of these features and thereby expand their behavior repertories. Nehring (71) built a maze in a pig pen. McGlone and Curtis (67) provided pigs hiding places for their heads allowing them to submit to and subsequently avoid an aggressive pen mate. Fraser provided pigs a mezzanine for use in getting away from group mates (19, 74). Grandin (40) enriched pig environments with suspended manipulanda (pig toys). Pigs reared in enriched environments proved easier to be moved about than pigs in traditional production environments (43). Pigs residing in pens equipped with suspended manipulanda fouled their feeder markedly less often than did those in a relatively barren environment (92).

From the above, it might be inferred that animals in richer natural or artificial environments behave differently and experience an enhanced sense of well-being compared to those in more barren surroundings. But this has not been determined scientifically to be the case, and many questions persist. For example, do pigs enjoy a higher sense of well-being when able to use enriched features'? Are they starved for stimulation in less rich environments'? If so, does this lead to a craving for stimulation'?

Commercial gilts and sows often reside during pregnancy in rectangular crates that prevent them from turning around. When living in a crate shaped so as to permit her to turn around, a pregnant gilt will turn around approximately 13 times daily in a crate 61 cm wide, but only 9 times daily in a 56 cm wide crate (in which it is more difficult for the gilt to turn around) (63). Little is known about what motivates a gilt to turn around. Does she need to turn around'? Does this need affect her productive performance'?

How an animal perceives its living space may be crucial to its sense of well-being. Sometimes space can be modified physically or rearranged so as to make it more accommodating to the animal. For example, animals in pens have a propensity to keep their heads at or to lie around the perimeter of a pen instead of in the middle (39, 90). A triangle has 28 percent more perimeter and a square 13 percent more than a circle of equal area. Thus, of the three, triangular pens maximize the ratio of perimeter to area. Should animal facilities be built with triangular pens and cages instead of rectangular ones to enhance the animals' comfort'? Is it necessary to have more space in a rectangular pen to engender the same feeling of well-being that an animal would experience in a square pen of equivalent perimeter'?

Learned Helplessness— Animals often encounter frustrating situations and presumably these may decrease their well-being. For example, when anything gets in the way of an animal on its way to the feeder to eat, that animal becomes frustrated. Frustration is one of the prepathological states indicative of stress (69). Frustrating situations generally are stressful, as indicated by various physiological indicators (13).

Farm animals may be frustrated when engaged in any strongly motivated behavior pattern, whether eating, nesting, and engaging in sexual activities, among others. Depending on the circumstances, for example, frustrated hens may show displacement behavior—behavior patterns that occur out of context with preceding and succeeding behavior (16).

In other settings, an animal may find that it can neither control its environment nor predict what its environment will be, and the animal may learn to act in a helpless manner. In a state of learned helplessness, an animal stops initiating behavior aimed at controlling or making use of environmental features because it has learned to expect that these features are uncontrollable and that these attempts would be futile (84).

Animals residing in certain intensive production systems might well learn to expect that they have little or no control over their surroundings. It is possible that agricultural animals living in certain housing systems may develop learned helplessness (14, 61. 62). Learned helplessness would be another of the prepathological states indicative of stress (69).

Nestbuilding—Females of all domestic avian species build nests in which they lay their eggs. The domestic hen will engage in nest-building every day, even when a previous nest exists. It seems that the performance of nest-building is itself positively reinforcing to the hen (50).

Most sows attempt to construct a farrowing nest beginning 12 to 16 hours prior to delivering the first pig, regardless of where they are (51). In many modern farrowing environments, there is neither the space in which to conduct nest-building behavior nor the material with which to build a nest. Sows nevertheless direct substantial amounts of time toward small amounts of material even though a nest may not result. This suggests that for the sow, as for the hen, nest-building behavior in itself is rewarding (99). Research is needed to answer such questions as: Do hens and sows need to build nests'? How much frustration do they experience when they either cannot move enough material to nest-build or cannot find nesting material? How do they feel when they cannot build a nest? Does this feeling in sows result in hormonal changes that are an anathema to oxytocin's actions in birth and lactation'?

Electro-Immobilization— Animal may find certain procedures routinely performed in agricultural production to be uncomfortable or even painful. When an animal actively avoids a procedure it is presumably revealing negative feelings about the procedure. Ewes having experienced restraint by electro-immobilization and by a squeeze-tilt table, when given the choice between the two in a Y-maze avoid-avoid test, chose the squeeze-tilt table 79 percent of the time, and the electro-immobilizer 13 percent (42). Questions that need answers include: What was the ewe thinking as she hesitated at the decision point, indicating by her head movements that she is vacillating? Was she actually imagining the feeling she experienced during electro-immobilization earlier'? Based on the ewe's reactions, when should the electro-immobilizer not be used? What behavior indicators identify the point beyond which it would be inhumane to continue subjecting the ewe to the procedure?

Photo credit: University of Illinois

The sow—in anticipation of delivering a litter of piglets within a few hours—is building a maternal nest to protect the piglets from cold and predators.

Chicken-Harvesting Machine— Animals can adapt in a matter of seconds to machines with which they are forced to interact, provided that the machines are designed with the animal's nature in mind. Take, for example, the chicken harvesting machine developed in the United Kingdom. The harvesting of birds from growing houses is a monumental task. Moreover, considerable

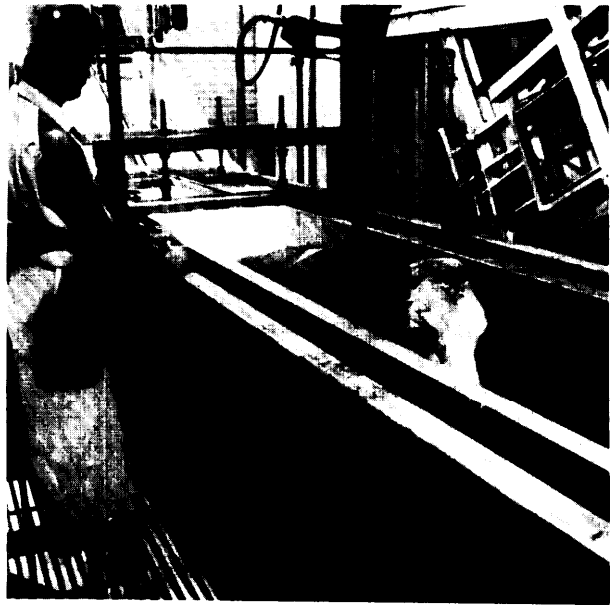
losses are incurred in the process of harvesting and transportation, especially in the hand-catching and hand-crating processes (25).

A prototype chicken-harvesting machine has been evaluated in terms of the stressfulness of the harvesting process (15). By means of electrocardiograms and immobility tests, it has been found that the stress from harvesting could be reduced by catching and picking up broiler chickens with a carefully designed machine, rather than by hand. Heart rate dropped back to normal more quickly and duration of tonic immobility (a phenomenon that increases with fear) was much shorter in machine-harvested birds than in those caught by hand. Research questions include: What is a chicken thinking when it is manually caught by one leg and carried upside down to the crate in which it will be transported to the processing plant'? How does this contrast to what it is experiencing when it is caught by the long rubber fingers of a chicken-harvesting machine, moving it onto a moderately inclined conveyer belt, which it rides to the gathering stage'?

Double-Rail Restrainer Conveyor **System—Means** of rapidly moving large numbers of animals of all kinds are needed in the production and processing industries. The V-restrainer, in which animals are moved along and wedged between two v-angled conveyor belts, with their legs dangling, is a vast improvement over driving animals through a chute, but it gives rise to additional problems.

A prototype of this system was developed in the late 1970s, and it caused little premortem stress in animals when used in a processing plant (98). The system was further developed for applications ranging from veal, lamb, and swine slaughter lines to feedlot cattle processing. When designed specifically for the species and size range to be handled, the animals apparently find the conveyer belt comfortable to ride. Adjustable sides prevent the animal from leaning sideways which is important because tilting sideways seems to frighten the animal.

As the above discussion illustrates, there are many questions to be answered regarding animal welfare. Of particular importance is the effect of animal well-being on the animal's performance. Some research seems to indicate that the amount of psychological stress an animal experiences determines how the pituitary-adrenal axis responds. In other words, psychological stress may be reducing the animal's performance as well as the animal's well-being. Much more research is needed to understand such relationships. To date, little research has been done in the United States on animal well-being.



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Biotechnology and Farm Animal Well-Being

In the past few years, animal protection groups have begun to voice concerns about biotechnology. Their concerns are rather diffuse and it is difficult to determine precisely what could be done to address those concerns. The new techniques for manipulating genetic material strike at some deep-seated fears amongst animal protection groups. While there are few concise papers explaining animal protection concerns, a reading of the relevant literature leads to the identification of the following issues:

. reinforcing notions of animals as mere property to be manipulated at the whim of human owners, and
. animal well-being issues (81).

Manipulation of Property

Genetic engineering conjures up images by some in the animal protection movement of animal machines being reconstructed by ingenious scientists to meet human needs. The push to be allowed to patent animals (discussed in ch. 15) merely reinforces the idea of animals as patentable machines. At a time when the animal movement is pushing to increase the moral status of animals to, at the very least, something between persons and property, the biotechnology era and patenting seem to be a major step backwards.

Animal Well-Being Issues

The impact of biotechnology on animal well-being is probably the most challenging issue genetic engineering raises. The technology is most likely impact-neutral in that one could use biotechnology to improve animal well-being (e.g., engineer disease resistance, eliminate detrimental genes from a population) as well as compromise it. The clearest example of compromised well-being is the "Beltsville pig" (discussed in ch. 3). This pig is the result of research at the U.S. Department of Agriculture (USDA) in Beltsville that involved the insertion of extra growth hormone genes. When the extra genes were expressed, the animal grew fast but, as it gained weight, it became lame and lethargic and suffered from degenerative joint disease and a variety of other disorders (41). There is little doubt that the animal was under stress as a result of the genetic manipulation. Questions also have been raised about the quality of life for the "oncomouse' and some of the other mice that have been developed to shorten the time of standard carcinogen and mutagen tests.

It is also possible, however, that some genetically engineered animals might reduce the need for research animals and hence qualify as alternatives. Among farm animals, moreover. it may be possible to use genetic engineering to eliminate the horn gene in cattle, thereby removing the welfare problems associated with dehorning (4 1). While some object strongly to the proposal that farmers should create breeds of microcephalic (small brained) farm animals that are quite content in close confinement (41), others say that as long as the animal is in a state of positive well-being, such a creation would not be morally objectionable though there may be some esthetic problems with such creatures (79). To date, there has been little discussion or debate of these questions. and about the most that can be concluded at this stage is that careful monitoring of transgenic animals to determine their state of well-being is essential. As more experience and research with transgenic animals takes place, it will be possible to develop more sensible guidelines and conclusions.

Biotechnology is a *priori* neither good nor bad for animals. Its impact depends on what is done and its effect. If it is used judiciously to benefit humans and animals, with foreseeable risks controlled, and the welfare of the animals is kept in mind, it is morally defensible and can provide great benefits.

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Part III

Environmental Quality

Chapter 7

Environmental Issues: Institutions and Their Regulatory Roles

Photo credit Jamie Notter, OTA Staff

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INTRODUCTION

Preface

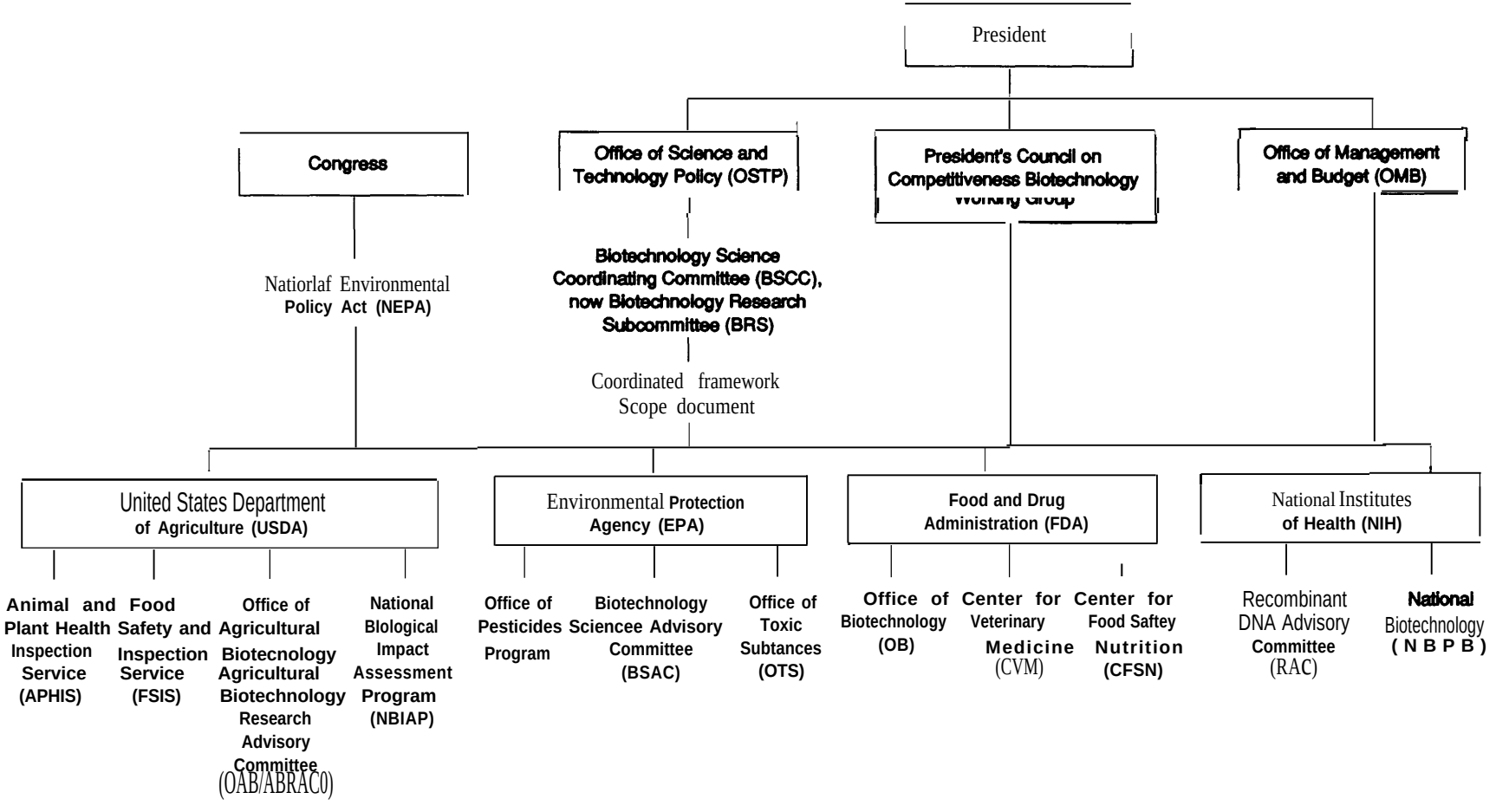
Many biotechnology products, especially agricultural products, are intended for use in the environment. Examples are transgenic cows in feed lots, insect resistant crop plants in fields, microbial pesticides applied to cropland, and transgenic fish reared in outdoor aquiculture ponds. **Virtually anything introduced into the environment will have an impact,** whether it be concrete slabs used to construct a highway or a chemical pesticide used to control insects on cotton. The task of environmental protection legislation is to determine what types of products to be used or activities to be carried out in the environment would have adverse effects significant enough to warrant regulation. Ideally, Federal environmental protection laws and regulations would be based on complete information on all the environmental risks associated with products and activities as well as their benefits, so that decisionmakers could weigh one against the other objectively. In reality, complete information is rarely available, particularly for new products: thus, the balancing of risks and benefits is difficult and open to bias.

Biotechnology has appeared on the scene during a time of intense environmental and political scrutiny of new technologies. Oversight of biotechnology thus is significantly different from that of emerging technologies in the past and may foreshadow the reception of new technologies in the future. For example, planned introductions of recombinant DNA-modified organisms will occur in a regulatory climate vastly different from that which existed as dramatically new crop varieties were introduced in the past. Key policy documents to be discussed later (e. g., 1986 Coordinated Framework statement of Federal agencies' philosophy on biotechnology, and the Council on Competitiveness' report on Administrative philosophy) stress the need to regulate biotechnology only on the basis of the risk of its products. not simply because it entails the new process of recombinant DNA technology. Tension exists, however, between this philosophy and operational development of oversight treatment. This tension often seems to be triggered by the technology itself, and has led to controversy over regulation of field tests. Special regulatory attention to a new agricultural technology could have implications for environmental safety and for the successful adoption of that technology and thus for U.S. economic competitiveness.

Most agricultural biotechnology products intended for use in the environment are or will be regulated according to legislation enacted prior to the advent of modern biotechnology, including laws intended to protect agriculture and the environment from chemical contamination, plant pests, pathogens, and so on. Despite the unusual level of scrutiny focused on biotechnology, its oversight is meant to arise naturally from the responsibilities traditionally held by different offices or services within the Environmental Protection Agency (EPA) and the U.S. Department of Agriculture (USDA). Given the panoply of laws applicable to biotechnology. this chapter provides a road map through the confusing territory of oversight responsibilities.

Figure 7-1 is the reference point used throughout the chapter. It gives a capsule overview of roles and relationships of policymaking bodies, key documents relating to designation of authority over environmental uses of biotechnology products, agencies with regulatory authority, the specific services or offices involved in regulation of biotechnology, and statutes that pertain to the use of biotechnology products in the environment. Following an introductory description of why and how regulation and oversight for biotechnology products has evolved, this chapter describes USDA's and EPA's role in these activities. The complementary roles of the Food and Drug Administration (FDA), National Institutes of Health (NIH), and State and local governments, as well as the international regulatory climate also are covered. Finally, policy issues are discussed here, among them issues of jurisdiction and coordination among agencies, scope of coverage, potential impacts of regulation on research and on agribusiness, and public participation. (See also OTA, 1988 New *Developments in Biotechnologg 3, Field Testing Engineered Organisms." Genetic and Ecologic Issues (102)* and 1991 *Biotechnology in a Global Econony) (103).* This chapter lays the foundation for ensuing discussion (ch. 8) of risk assessment and risk management issues related to impending large scale, commercial uses of agricultural biotechnology and biocontrol products.

Figure 7-l—Jurisdiction and Coordination of Environmental Policy for Biotechnology-Derived Agricultural Products[a]



USDA statutes
- Plant Pest Act
- Plant Quarantine Act
- Noxious Weed Act
- Vims-Semm-Toxin Act
- Federal Meat Inspection Act
- Poultry products Inspection Act

EPA statutes
- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- Toxic Substances Control Act (TSCA)

FDA statute
- Food, Drug, and Cosmetic Act (FDCA)

[a]OSTP, Council on Competitiveness, and OMB do not have direct oversight of the Federal agencies; the connections shown are those of influence through directives, key policy documents, or review.

SOURCE: Office of Technology Assessment, 1992.

Agriculture, Field Trials, and Deliberate Release of Genetically Engineered Organisms

Progress in agriculture traditionally has depended on selection of the best of new varieties based on field testing of cultivars. The seed industry views cultivar field testing as an essential part of cultivar development programs. The main purpose of field testing is

> . . . to determine the regional environmental adaptability and market fit of the new cultivars or hybrids to know whether the items to be tested have the required disease resistance for the areas, whether they meet the needs of the industry as far as type or quality is concerned. and whether they will perform well under the environment of the region (98).

Field tests also can provide evidence that the application of currently available scientific principles and information can ensure safe commercialization of new products.

Genetically modified organisms, like any other organisms, must be field tested in the environment in which they would be cultivated. For example, whether the engineered trait is expressed effectively must be evaluated in condition-s representative of those the cultivated crop will encounter. Characteristics intended to confer drought tolerance to a plant. for instance, must appear and function effectively within the plant as it copes with representative drought-stressed environments. Greenhouse experiments, conducted in facilities designed to meet containment specifications, can provide only an initial screening; the field trial is an essential evaluative step.

Brief Overview of Concerns

As necessary and rational as field testing is, concerns have arisen over any release of genetically engineered organisms. Living creatures reproduce themselves; they may increase in numbers; and they may even exchange genes with other wild organisms. Many are worried in particular about the uncertain possible impacts that an organism with a new trait might have on other species in the local habitat.

Evolution of Regulation and Oversight

These concerns and uncertainties have stimulated efforts to articulate regulatory oversight; the spelling out of jurisdiction in the Coordinated Framework for the Regulation of Biotechnology [51 Federal Register (FR 2302-23393] (77) was a significant step in the organization of regulatory oversight. This fundamental document outlining the roles, responsibilities, and policies of the Federal agencies involved in biotechnology first actually appeared in the Federal Register in 1984, when the Domestic Policy Council of the White House announced the ''Coordinated Framework for the Regulation of Biotechnology" (49 FR 50856-50907). The framework set forth certain premises, which have guided subsequent policy:

- previously existing knowledge was regarded as pertinent,
- existing laws were for the most part regarded as adequate for biotechnology oversight, and
- different biotechnology products were regarded as falling under the mandate of different agencies (table 7-1).

Other key points of the framework include the following:

- the products of biotechnology, not the process itself, would be regulated; and
- biotechnologically altered organisms are not fundamentally different from nonmodified organisms (although the introduction to the framework recognized that certain microbial products would require the establishment of additional regulatory requirements).

The framework included a compilation of existing laws, regulations, and guidelines that are potentially applicable to biotechnology, policy statements from the regulatory agencies on how they intend to apply their existing regulatory authority to biotechnology, and proposed criteria for determining what should be subject to oversight.

In a basic sense, agencies draw their authority to evaluate ramifications of the new technology based on their own mandates, and from the National Environmental Policy Act (NEPA). (See box 7-A.) Since the framework **was** introduced, agencies have accumulated experience with deliberate releases; based on this experience, they are continuing to refine their regulatory roles. As of September 1991, USDA-APHIS (Animal and Plant Health Inspection Service), which oversees most plant-related work and animal biologics, has issued some 181 permits for field testing of genetically engineered plants or microorganisms (not including veterinary biologic). At least half of these have been issued since the beginning of 1990. (See table 7-2.)

USDA permits issued for transgenic plants with pesticidal properties have been informally reviewed by the

Table 7-l—Jurisdiction for Review of Planned Introductions in Research

Proposed research	Responsible agencies
Contained research, no release in environment	
Federally funded	Funding agency,[a]
Nonfederally funded	NIH or S&E voluntary review, APHIS[b]
Foods and food additives, human drugs, medical devices, biologics, animal drugs	
Federally funded	FDA,[c] NIH guidelines and review
Nonfederally funded	FDA.[c] NIH voluntary review
Plants, animals and animal biologics	
Federally funded	Funding agency,[a] APHIS[b]
Nonfederally funded	APHIS,[b] S&E voluntary review
Pesticide microorganisms	
Genetically engineered	
Intergeneric	EPA,[d] APHIS,[b] S&E voluntary review
Pathogenic intrageneric	EPA,[d] APHIS,[b] S&E voluntary review
Intrageneric nonpathogen	EPA,[d] S&E voluntary review
Nonengineered	
Nonindigenous pathogens	EPA,[d] APHIS
Indigenous pathogens	EPA[d] APHIS
Nonindigenous nonpathogen	EPA[d]
Other uses (microorganisms) released in the environment	
Genetically engineered	
Intergeneric organisms	
Federally funded	Funding agency,[a] APHIS,[b] EPA[d]
Commercially funded.	EPA, APHIS, S&E voluntary review
Intrageneric organisms	
Pathogenic source organisms	
Federally funded	Funding agency,[a] APHIS,[b] EPA[d]
Commercially funded.	APHIS,[b] EPA[d] (if nonagricultural use)
Intrageneric combination	
Nonpathogenic source organisms	EPA Report
Nonengineered	EPA Report,[e] APHIS[b]

[a]Rewiew and approval of research protocols conducted by NIH, S&E, or NSF.
[b]EPA jurisdiction for research on a plot greater than 10 acres.
[c]APHIS issues permits for the importation and domestic shipment of certain plants and animals, plant pests and animal pathogens, and for the shipment or release in the environment of regulated articles.
'EPA reviews federally funded environmental research only when it is for commercial purposes,
'Designates lead agency where jurisdictions may overlap.

KEY:NIH - National institutes of Health; S&E = U.S. Department of Agriculture Science and Education; APHIS = Animal and Plant Health Inspection Service; EPA = Environmental Protection Agency; NSF = National **Science Foundation**

SOURCE: 51 Fed. Reg. 23305 (Office of Technology Assessment, 1988).

EPA Office of Pesticide Programs under an interagency agreement. EPA has reviewed a total of 94 notices for field tests of microorganisms since the framework was published in 1986, 74 of which were for microbial pesticides. Under an interagency agreement, EPA has in addition provided comments on approximately 100 permits submitted to USDA-APHIS for transgenic plants with pesticidal properties. (See table 7-3.)

These field tests provide the foundation of information and regulatory experience for decisions regarding full-scale agricultural use of transgenic organisms. This report comes at a critical point in the evolution of agricultural biotechnology, as it moves from the laboratory toward large-scale commercialization and use.

USDA

Authority for Plants

Statutory Authority

The Animal and Plant Health Inspection Service, APHIS, was established in 1972 as a regulatory agency within USDA with responsibilities for protection of the environment. APHIS unites the programs within USDA designed to protect American agriculture from destructive pests and diseases. APHIS' activities include the development of exclusion procedures to keep pests and diseases out of the United States; and monitoring, de-

Box 117-A–The National Evironmental Policy Act (NEPA)

The National Environmental Policy Act (NEPA) is the sole Federal law that is broadly applicable to all agencies and departments involved in the research or regulation of biotechnology products intended for use in the environment. Enacted in 1970, NEPA is a reflection of increasing concern about environmental quality and calls for a "balance between population and resource use which will permit high standards of living and a wide sharing of life's amenities" [section 101(b)(5)]. NEPA requires that any agency decision on a major Federal action significantly affecting the quality of the human environment include consideration of the environmental impact of the proposed action and alternatives to the proposed action. NEPA does not, strictly speaking, restrict or prohibit any activity that may adversely impact the environment but rather outlines procedural requirements by which Federal agencies must become aware of and consider the environmental consequences before making a decision on a proposal.

The Council on Environmental Quality (CEQ) is responsible for the implementation of NEPA (CEQ Final Regulations for Implementing NEPA, 43 Fed Reg 59978, 1978), but the specific method used for compliance by individual agencies is broadly discretionary. Because EPA's mission is to consider and protect the environment through its regulatory activities, most EPA actions are considered the functional equivalent of NEPA compliance. [Warren County v. North Carolina, 528 f. Supp. 276,286 (eDNC 1981)]. Most other Federal agencies have issued their own regulations to implement NEPA.

Although agencies are given broad discretion in how they evaluate and balance environmental impacts in making decisions, NEPA does open agency actions to public and judicial scrutiny. The establishment and protection of certain environmental values by NEPA gives public interest groups and private individuals standing to bring suit to ensure compliance even though they are not directly affected by an agency action. In short, NEPA has had two principal impacts on the Federal decisionmaking process: ensuring evaluation of environmental issues by Federal agencies and increasing public participation.

SOURCE: Office of Technology Assessment, 1992.

tection, eradication, and control programs to control the movement of pests and the spread of disease. APHIS operates under a myriad of legislative authorities, some dating back to 1884.

Under the Coordinated Framework, APHIS is designated the lead agency responsible for the regulation of plant and animal biotechnology products. The assumption underlying this jurisdictional determination was that

> Agriculture and forestry products developed by biotechnology will not differ fundamentally from conventional products and that the existing regulatory framework is adequate to regulate biotechnology (51 Fed. Reg. 3123, p. 23302).

The primary regulatory authorities available to USDA that are most applicable to biotechnology (and the environment) are the Federal Plant Pest Act, the Plant Quarantine Act, the Noxious Weed Act. the Virus-Serum-Toxin Act. the Organic Act, the Federal Seed Act, the Federal Meat Inspection Act. and the Poultry Products Inspection Act. Of these statutes, two are used as the basis for the regulation of the environmental release of genetically modified organisms: the Federal Plant Pest Act, and the Plant Quarantine Act (7 CFR 340). Like the Noxious Weed[2] Act, these two acts are exclusionary statutes intended to prevent the entry into or dissemination within the United States of living organisms considered dangerous to American agriculture. These three legislative authorities traditionally have been used as the basis for inspection, quarantine, and pest eradication programs of the Division of Plant Protection and Quarantine. With the exception of the Noxious Weed Act, they now also are used by the Division of Biotechnology, Biol-

[1] A Plant Pest is defined as any living stage of: any insects, mites, nematodes, slugs, snails, protozoa, or other invertebrate animals, bacteria, fungi. other parasitic plants or reproductive parts thereof, viruses or any organisms similar to or allied with any of the foregoing, or any infectious substances. which can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or any processed, manufactured, or other products of plants.

[2] "Noxious weed" is defined as any living stage (including but not limited to, seeds and reproductive parts) of any parasitic or other plant of a kind, or subdivision of a kind. which is of foreign origin, is new to or not widely prevalent in the United States, and can directly or indirectly injure crops, other useful plants. 1 ivestock, or poultry or other interests of agriculture, including irrigation. or navigation or the fish or wildlife resources of the United States or the public health.

Table 7-2—Federally Approved Biotechnology Agricultural Research Field Test Applications, USDA (through September 24, 1991)

	Private	Public
1987	9	0
1988	17	1
1989	31	7
1990	42	15
1991	47	12
Total	146'	35[b]

[a]41 tomato; 23 cotton; 17 tobacco; 14 corn; 13 potato; 13 soybean; 10 cantaloupe/squash; 6 alfalfa; 4 clavibacter/corn; 1 clavibacter/rice; 1 TMV/tobacco; 1 rapeseed; 1 sunflower; 1 chrysanthemum.
b 11 potato; *9 tobacco; 3 cucumber; 3* rice: 2 pseudomonas; 2 walnuts; 2 xanthomonas; 1 tomato; 1 poplar; 1 alfalfa.

SOURCE: APHIS BBEP Biotechnology Permits Unit, *Issued Permitss List,* Sept. **24, 1991.**

Table 7-3—Federally Approved Biotechnology Agricultural Research Field Test[a] Applications, EPA (through April, 1991)

	Total	Repeats
Office of Toxic Substances	20[b]	7
office of Pesticide Programs , ...	74"	34

'Field tests of microorganisms reviewed by EPA since the publcation of the 1986 Coordinated Framework.
b 10 Rhizobium, 8 *Bradyrhizobium, 2 Pseudomonas.*
[c] Includes a variety of bacteria, fungi and viruses, both nonindigenous and genetically modified

SOURCE: David Giamporcaro, Environmental Protection Agency, **personal communicatlon,** Oct. 18, 1991.

ogics. and Environmental Protection [established in October, 1988] to regulate the movement and environmental release of genetically engineered organisms.

The Noxious Weed Act has not been used to regulate genetically modified organisms. The applicability of the Noxious Weed Act to genetically modified organism is limited by the requirement that the plant be of "foreign origin' and the requirement that an organism be placed on the noxious weed list before it can be regulated.

The Federal Plant Pest Act. the Plant Quarantine Act, and the regulations issued to implement them are not intended to present unreasonable barriers to commerce. For example, inspection at ports of entry should be expedient so as not to retard shipment of agricultural products, particularly fresh produce whose value could be diminished or destroyed if the product to be inspected is held at the inspection station too long.

Agency Interpretation/Regulatory Policy

USDA's overall philosophy regarding biotechnology products is articulated in the National Academy of Sciences 1987 publication, *Introduction of Recombinant DNA-Engineered Organisms into the Environment: Key Issues (72);* and in the National Research Council 1989 publication, *Field Testing Genetically Modified Organisms." Frumework for Decisionmaking (73).* Consistent with U.S. Federal policy, USDA-APHIS bases its regulatory policy on certain key premises:

1. the products of biotechnology do not differ fundamentally from either unmodified organisms or conventional products,
2. the product should be regulated rather than the process by which it came to be,
3. end-use of the products and review conducted on a case-by-case basis should form the basis for regulation, and
4. sufficient authority for regulating the products of biotechnology is provided by existing laws.

Along with these premises is a commitment to the safe development of the new technology, and to a balanced, scientifically based and risk-based regulatory framework that protects agriculture as well as facilitates technology transfer (55).

The USDA regulations (7 CFR 340), that pertain to genetically engineered organisms are applicable to a broad range of organisms, including

> Any organism which has been altered or produced through genetic engineering. if the donor organism. recipient organism. or vector or vector agent belongs to **any genra** or taxa designated ...and meets the definition of plant pest. or is unclassified. . or any other organism or product altered or produced through genetic engineering which the Deputy Administrator deterrmines is a plant pest or has reason to believe is a plant pest.

Excluded are microorganisms that are not plant pests and produced by the addition of well characterized or noncoding regulatory regions.

Any person may petition to amend the list of organisms subject to regulation under 7 CFR 340. Such a petition must include the factutal grounds as to why the organism is not a plant pest and include scientific literature in support of this conclusion. Petitions should not include Confidential Business Information (CBI). The petition also should include any information known to the petitioner that would be unfavorable to the petition. APHIS then publishes a notice in the Federal Register for comment. A must respond to the petitioner within 180 days either by approving or denying the petition in whole or in part. Once an organism or class of organisms is delisted, it may move unhindered in commmerce with no

reporting requirements or monitoring required by the Federal Government. If, however, new information becomes available that leads the Secretary of Agriculture to conclude that a delisted organism does, in fact, pose a plant pest risk, an interim rule can be issued, effectively bringing that organism back under regulatory authority of the Federal Plant Pest Act.

It is unclear whether industry will try to petition to exempt broad classes of organisms or single. well-defined organisms. Initially some industry executives thought that they might like to delist broad classes; but some have since reevaluated this approach since the organism-by-organism delisting procedure is a market barrier to competitor-s. Broad class delisting might make it easier for some competitors to enter commerce. Furthermore, APHIS approvals provide a ''stamp of approval useful in acceptance by the public and by State governments. In addition, environmentalist groups might pose a legal challenge to stop a broad class delisting under the Federal Plant Pest Act.

Implementation

Under the APHIS regulations. anyone wishing to move or introduce an organism fitting the definition of a regulated article must receive a permit. The four kinds of permits for which applications are made are as follows:

1. a permit for release into the environment (application submitted 120 days in advance).
2. a single 1 -year permit for interstate movement of multiple regulated articles between contained facilities,
3. a single 1 -year permit for importation into the country of multiple regulated articles into contained facilities, and
4. a courtesy permit to expedite movement of organisms not subject to regulation under 7 CFR 340 (application submitted 60 days in advance) (55)

Permit applications require submission of information on the biology of the donor and recipient organisms. the molecular biology of the introduced gene(s), and plans for containment during the trial and post-trial clean-up. Information is used by APHIS to prepare an Environmental Assessment (EA) and to determine whether and under what conditions to allow the release.

The application process for Environmental Release permits is clearly delineated by USDA-APHIS, with process and pemmitting requirements contained in *Plant Pests,. Introduction of Genetically Engineered Organisms of Products, Final Rule (52* FR 22892 (1987). In addition, Biotechnology, Biologics and Environmental Protection (BBEP). USDA-APHIS. has developed a User's *Guide for Introducing Genetically Engineered Plants and Microorganisms to* provide assistance to those submitting applications for a permit under 7 CFR 340. The folloowing steps must take place:

1. completing an application for permit under 7 CFR 340, Genetically Engineered Organisms or Products. APHIS Form 2000:
2. assigning an accession number;
3. preliminary pest and environmental assessment;
4. state review/input;
5. site inspection;
6. issuance or denial:
7. appeal. if permit request has been denied: and
8. inspection of site at initiation of experinment.

From day one, scientific review proceeds. The State authorities are forwarded material by day 30 and respond by day 60. At or before day 120. the biotechnology permit is issued or denied (104).

Scientific review is based on the dutti provided in response to the APHIS permit application data requirements. Fourteen such requirements (box 7-B) include a detailed description of' the organism. the location of' the field test, and containment protocols.

Provision is made for companies to protect Confidential Business information: they can submit both a full proposal and one for public abvailability that has CBI deleted. The APHIS Policy Statement on the Protection of Privileged or Confidential Business Information (50 FR 30561 -63) delineates data or information, such as trade secrets and confidential commercial or financial information, that can be protected from disclosure under section (b)(4) of the Freedom of Information Act (5 U.S.C.552 (b)(4). This can include production data, formulas and processes, and quality control tests and data, along with research methodology and data generated in the development of the production process. To qualify as CBI, this information must be: 1) commercially valuable, 2) used in one's business. and 3) maintained in secrecy. Furthermore, APHIS must be persuaded on review of information on competition that significant commercial harm would result from disclosure. BBEP explains this option to applicants, while encouraging them to be selective as to what truly calls for CBI designation (63). APHIS requires claims of Confidentiality to be substantiated at the time of submission.

An Environmental Assessment (EA) is prepared by APHIS in accordance with the provisions of the National

Box 7-8—The 14 Types of Information Requested by APHIS in a Permit Application for Genetically Engineered Plants. 7 CFR 340

1. Information on responsible person and type of permit requested, such as movement or release.
2. All names (scientific, common, and trade) and designations necessary to identify the donor, recipient, vector, or vector agent constituents of the transgenic plant.
3. Information on the persons who developed the transgenic plant.
4. Movement of the plant.
5. The anticipated or actual expression of the altered genetic material in the plant and how the expression differs from the nonmodified plant in respect to characteristics such as morphology, physiology, number of copies of the gene, products, etc.
6. The molecular biology of the system used to produce the transgenic plant—donor, recipient, vector, or vector agent.
7. Country and locality where the donor, recipient, vector, or vector agent were collected, developed, and produced.
8. The purpose of the experiment and the experimental design.
9. The quantity, schedule, and number of introductions.
10. The processes, procedures, and safeguards used to prevent contamination, release, and dissemination in the production of the transgenic plant.
11. The intermediate and intended destinations of the product; the field trial site.
12. Safeguards to prevent dissemination at each site.
13. Biological material accompanying the plant, such as inoculum or soil.
14. Method of disposal of plant material after termination of the experiment, such as autoclaving or discing.

SOURCE: S. McCammon and T. Medley, "Certification for the Planned Introduction of Transgenic Plants in the Environment," The Molecular and Cellular Biologics **of the Potato, Michael Vayda and William Park (eds.), Wallingford, U.K. (CAB. International), 1990.**

Environmental Policy Act (NEPA) of 1969 (42 U.S.C. *4332 (1970)).* Among the components of the EA are procedural and physical precautions against risk, environmental consequences, and background biology. The development of the EA is a process intended to assure public safety.

A permit to move or introduce an organism is issued if there has been a Finding of No Significant Impact (FONSI) from **such** action, and a full-scale environmental impact statement is not required. Notice of the action and the availability of the EA and FONSI is published in the Federal Register. Special additional conditions may be added to the permit that require monitoring and data collection to ensure containment. Such test data can also contribute to the information base from which future assessments can draw. The issuance of the permit constitutes certification by APHIS that no significant risk exists to the environment or to agricultural crops from the action. Recommendations for improving APHIS assessments have included making justifications for assessment conclusions more explicit, including more opportunities for gathering data on gene flow and weediness during field tests, and encouraging more timely and complete monitoring reports (110).

Application to Plants

Small-Scale **Research**

Theory— Small-scale releases in the form of field trials are experiments. Even if companies conduct them, and although field trials are the first step toward full-scale agricultural use in the environment, they are nonetheless still research rather than commercialization activity. This activity raises some concerns, but these are, to some extent, alleviated by the small scale of field trials. The first release into the environment of an organism with a novel trait can arouse concerns simply because something relatively new is happening. The regulatory policies and procedures described above represent an attempt to address such concerns. However, given the low numbers of organisms involved, the small-scale field trial is quite a carefully controlled situation. In fact, some argue that USDA requirements for most field tests exact financial, administrative, and time costs that are disproportionate, relative to any risks presented. USDA-APHIS views the small-scale field trial as playing an educational role; data compiled from these tests will provide the underpinnings for sound and rational assessment of large-scale releases in the future. As noted earlier, each permit issued for a

small-scale field trial requires the submission of subsequent data.

One of the players in the oversight of field trials is the Office of Agricultural Biotechnology (OAB), which was established in 1987 under the Deputy Secretary of Agriculture and transferred to the Assistant Secretary for Science and Education in 1989. OAB is designed to ensure coordination of biotechnology activities within USDA. Within Science and Education, it is separate in many ways from APHIS. It provides staff support for the USDA Committee on Biotechnology in Agriculture (CBA) comprised of administrators of agencies: conducts outreach programs; and provides leadership in the development of guidelines and the dissemination of information about them. For example, a handbook, *Agricultural Biotechnology: Introduction to Field Testing was* produced in large part to help the "users" of the regulatory system in applications for field trials (11).

In line with its particular responsibility to provide guidance to researchers. the OAB staffs the Agricultural Biotechnology Research Advisory Committee (ABRAC) composed primarily of academic and industry scientists. Industry field tests. of course, are handled through APHIS. ABRAC was established in 1988 to provide advice for the Secretary of Agriculture, through the Assistant Secretary for Science and Education, on biosafety issues in the use of agricultural biotechnology and it has assisted in the development of biosafety guidelines, as well as case-by-case review of the minority of USDA-funded research projects that do not fall under other agency authorities. Its review process is modeled after that of the NIH Recombinant DNA Advisory Committee (RAC), with meetings open to the public and announced in the *Federal Register.* Two working groups established early in 1991 focus on the area of biotechnology risk assessment research as set out in the Farm Bill of 1990. These groups help set priorities and are developing a classification system and confinement protocols, integrating public comments received on the proposed guidelines for risk assessment research (70). *The Proposed USDA Guidelines for Research Involving the* ***Planned Introduction*** *Into the Environment of Organisms With Deliberately Modified Hereditary Traits was* published in the February 1, 199 Iissue of the Federal Register, part 3, with public comments due on April 2; a principal intent was to assist academic scientists and their institutional biosafety committees in the design of safe field trials.

USDA's Cooperative State Research Service established a new program in response to recommendations in a 1985 report of the National Association of State Universities and Land Grant Colleges' Committee on Biotechnology. NBIAP (National Biological Impact Assessment Program) has a mandate to facilitate safe field testing of genetically modified organisms and. thus, safe development of agricultural biotechnology. A principal charge to the program is to facilitate the appropriate application of knowledge derived from conventional field testing in the past to biotechnology field tests today. The program supports three areas of activity related to this function: information networks: facilitation of the development of biological monitoring techniques: and supper-t for biosafety research.

An information network to support the needs of public- and priate-sector researchers is being developed by NBIAP in conjunction with a number of institutions. The information network is available, over telephone lines, through an "800" number: through interlinked mainframe computers (BITNET): on floppy disks: and in printed format. An electronic bulletin board gives up-to-date information on biosafety related research activity and serves as the gateway for 14 databases. Individuals can use the network to communicate with other scientists as well. Databases include, among others: bibliographic and other listings; current literature; U.S. patents on genetically engineered species: current text of all Federal laws, regulations, and guidelines pertaining to biotechnology and biosafety; Institutional Biosafety Committee listings: and all approved applications for federally approved field test permits. licenses. and scientific reviews.

A knowledge base has been designed to help researchers identify the responsible Federal agencies to which an application should be directed and to prepare applications for permits, licenses, or scientific reviews. An ''intelligent form generator" will actually help the investigator prepare first drafts of applications. By dissembling information from existing knowledge. the intelligent form generator provides users with access to previously written standard text, technical descriptions, test-site information, and other resources from databases. Combining information with use of extensive menus leads to a technically specific application. The first, current version of the intelligent form generator is expected to be expanded from coverage of 8 groups of organisms to 79. The intent of the intelligent form generator is to lift some of the regulatory burden from the researcher. "Hyrpertext" information on biosafety is also provided.

A second function of the NBIAP is to facilitate biological monitoring of genetically modified organisms de-

literately released in the environment. NBIAP is surveying field studies that have been conducted; the information gathered should help guide future regulatory decisions. NBIAP also supports biosafety research on genetically modified organisms to improve understanding of their dispersal in the real world, and their impact on human health and the environment, to improve biosafety methods and to develop **useful prediction** models (51. 52).

Experience Base—Between July 16, 1987 and February 27, 1991, 102 permits were granted by APHIS for field testing of genetically engineered plants and microorganisms, along with 843 permits for importation or interstate movement of organisms regulated under 7 CFR 340. Twenty-one companies were issued permits by this date, including: Agricetus, Agrigenetics, Amoco Technology Co., Biosource Genetics, Biotechnica, Calgene, Campbell Institute for R&D, Canners Seeds, Ciba-Geigy, Crop Genetics International, DeKalb, DNA Plant Technology, DuPont, Frito-Lay, Monsanto, Northrup King, Pioneer, Rogers NK Seed, Rohm & Haas, Sandoz Crop Protection Corp., and UpJohn. Twelve research institutions. two of them USDA institutes, had received permits; they are: Auburn University; Iowa State University; Louisiana State University: New York State Agricultural Experiment Station (Geneva); North Carolina State University; Pennsylvania State; USDA-ARS (Agricultural Research Service), Albany, California: USDA-ARS, Fresno, California; University of California at Davis; University of Kentucky; University of Wisconsin; and Washington State University. Field trials were approved, with the agreement of the host State, for 33 States and Puerto Rico; the 102 permits granted as of February 27, 1991, gave rise to some 140 field test sites. By April 1991, 115 permits had been granted (78). By September 1991, 181 permits for field tests had been granted.

Figure 7-2 lists the new crop plants entering field trials between 1987 and early 1991, along with the novel characteristics, or genes expressed.

About half of the first generation of field tests, especially the 2 I in 1988, were for herbicide tolerance in tomato and tobacco. while the rest were almost entirely for disease and insect resistance in these two crops. Many more crops showed up in the 1989 applications, including potato, soybean. alfalfa, cotton, poplar, and cucumber: new sorts of characteristics included slowed fruit ripening and improved nutritional qualities. Modified pathogenic bacteria entered the applications in 1990, along with an increased range of cultivars and modifications, particularly in two of the country's most economically important crops, rice and corn (60).

Figure 7-2—Field Trials of New Crop Plants, 1987-91

1987-88	1989	1990	1991
Tobacco	Alfalfa	cantaloupe	Rapeseed
Tomato	Cotton	Corn	Sunflower
	Cucumber	Rice	
	Poplar	Squash	
	Potato	Walnut	
	soybean		

Genes expressed
- Herbicide tolerance
- Insect tolerance
- Virus tolerance
- Fungal tolerance
- Slowed fruit ripening
- Heavy metal sequestration
- Increased lysine production
- Antibiotic resistance

SOURCE: S. McCammon, U.S. Department of Agriculture, internal memo, 1991.

Biotechnica Agriculture. Inc., then a subsidiary of Biotechnica International, Inc., received in May of 1990 the first USDA approval to field test genetically engineered corn plants. The tests, to be conducted at the company's corn breeding station in Iowa. will analyze growth under field conditions and collect environmental data for future use. Biotechnica has coordinated other field tests, including one on tobacco with a gene coding for high levels of lysine expression (9). The company has applied for permission to conduct multiple field tests of corn engineered for improved nutritional quality; the gene transferred is one of several intended to improve corn for feed (4).

Northrup King has begun a 3-year field test of alfalfa plants genetically engineered to be compatible with a new herbicide claimed to be highly biodegradable and environmentally safe. With Monsanto. Northrup King has planted genetically engineered cotton in Hawaii to assess its resistance to various caterpillars (71).

An even longer term project was initiated by USDA-ARS researchers at the University of California-Davis. They inserted two marker genes into walnut tree embryos and will need to wait 5 years for the trees to reach maturity to assess expression brought about by the genes (76).

The first field trial of genetically engineered rice was approved at Louisiana State University. The test, taking place since June 1990 in a 110 *x* 63 foot plot in Baton Rouge, involves a marker gene and a transposon gene (that regulates gene movement) from corn (5).

USDA-ARS scientists are field testing potatoes with marker genes in Idaho, to see if the genetically engineered potatoes match the quality of conventionally bred products, under a permit issued in 1989. Some 1,000 potatoes, originally produced in a greenhouse from genetically engineered microtubers, are planted on a half-acre plot at the University of Idaho's research and extension center in Aberdeen (29).

Calgene successfully harvested field plots of its FLAVR SAVR tomato in the fall of 1990. Its permit for tomato plants engineered with an antisense gene for the pectalytic enzyme, or cytokinin pathway, was issued in May of 1990 (76). A complete listing of permits issued, applicants, organisms, and genes engineered along with date of issuance and location (State) is available in "Environmental Release Permits," printed by BBEP, APHIS, September 24, 1991.

Large-Scale Release

Theory-The USDA plans to use data from small-scale field trials to ensure the safety of large-scale releases. A variety of analyses and conferences are addressing the issue of large or commercial-scale release. For example, APHIS has organized the following three workshops to identify issues related to the large-scale use of genetically engineered crops in the environment:

1. Workshop On Safeguards for Planned Introductions of Transgenic Oilseed Crucifers, October 1990. Ithaca. New York;
2. Workshop On Safeguards for Planned Introductions of Transgenic Crops: Maize and Wheat. December 1990, Keystone, Colorado; and
3. Workshop on Biosafety Issues of Field Tests with Transgenic Potatoes, August 1991. St. Andrew's, Scotland.

A fourth workshop is planned for 1992 on biosafety issues for transgenic rice plants.

Experience ***Base—No*** commercial releases have yet occurred, nor have applications been made, although preliminary discussions have been held between company representatives and APHIS officials.

Authority for Veterinary Biologics

Statutory Authority

Under the authority of the Virus-Serum-Toxin Act (VSTA). as amended, USDA-APHIS regulates three cat. egories of veterinay bioiogical products derived through biotechnology. The establishment of these three categories was announced by APHIS in theJune 1986Coordinated Framework policy statement (51 FR 23339, June 26, [986). Based on that framework's premises that recombinant DNA derived products are not significantly different from more conventionally derived products and can be handled by a network of existing statutes, the three new categories were subsumed under VSTA's treatment of other biologics. APHIS supervises all experimental uses of veterinary biological products outside of containment conditions, under the provisions of the VSTA as amended by the Food Security Act of 1985. The implementing regulations (9 CFR 103.3) require approval from the Director of BBEP for shipment and describe required information for evaluating unlicensed biological products prior to granting such approval. APHIS also licenses biological products for unrestricted shipment in or from the United States under the VSTA, as amended.

Agency Interpretation and Regulatory Policy

The agency's policy is to balance control with flexibility in its review and approval procedures, and to adapt as necessary to new information. Products and organisms are categorized to provide practicable. reasonable procedures for review and approval: review takes place on a case-by-case basis.

Category 1 is comprised of inactivated (nonviable or killed) products prepared from recombinant DNA-derived vaccines. viruses. bacterins, bacterin-toxoids. viral subunits. or bacterial subunits. Monoclinal antibodies used prophylatically, therapeuticall y, or as diagnostics are also included. These products are viewed as presenting no risks to the environment or to safety.

Category 11 consists of products containing live microorganisms that have had one or more genes added (for expression of unique marker antigens or production of biochemical by-products) or deleted (i.e.. genes for virulence, oncogenicity, enzyme activity, or other biochemical functions). Such changes in genetic information must not lead to increased virulence, pathogenicity, survival advantages, or undesirable new or increased abilities to invade or survive in the animal host; and they must not compromise the safety characteristics of the organisms.

Under category III fall products that uselive vectors to carry recombinant-derivecl foreign genes coding for immunizing antigens or other immune stimulants. Live vectors may carry multiple such genes and successfully can infect and immunize the host. These organisms must be completely characterized and compared with the parent virus, and environmental and human or animal safety

concerns must be addressed in an Environmental Assessment or Environmental Impact Statement.

Implementation

As **with all other** veterinary biologics, recombinant DNA products must be shown to be pure, safe, potent, and efficacious, and not worthless, contaminated, dangerous, or harmful, with assurance of lack of negative effects on the environment and human and animal health prior to licensing. Additional information (e.g., demonstration of nonpathogenicity and nonreversion to virulence, or ability of the organism to maintain itself in a livestock population) may be requested. For recombinant-derived products the manufacturer also must report the cloned nucleotide sequence coding for the product.

For category 11 and 111 organisms, authorization procedures for shipping and guidelines for review of applications for field trials are done on a case-by-case basis. The categories of physical containment involved in movement of experimental products to the field are the following:

1. stringent containment conditions (level 4, isolation),
2. controlled environment (level 3).
3. Quarantined field conditions (level 2), and
4. Restricted field tests (level 1).

Unrestricted geographical distribution may occur only after issuance of a license.

In considering approval of these movements. APHIS requires four kinds of scientific information: human safety, ecological concerns, characterization of the vaccine virus, and animal safety. In addition, appropriate data would include: survival and reproduction of the engineered microorganism; interactions with other organisms; effects on the ecosystem if applicable; and scale, scope, and frequency of plasmid introduction. In short, an ecological risk assessment would include the biology of the phenotypic trait and of the parent organism, as well as characterization of the environment into which the introduction will be made; the product organism's host range and potential effect on other species might also be included.

The review cycle includes review and approval by an Institutional BioSafety Committee (IBC). State animal health regulatory officials and, if appropriate, public health officials. For trials with a small number of animals in quarantined conditions, APHIS must prepare a Safety Factor Evaluation assessing all parameters of the trial (*19).*

Application to Veterinary Biologics

Small-Scale Research

Theory—The theory underlying the approach to release of veterinary biologics is consistent with the National Research Council report (73) and the Scope Principles (i.e., that products of biotechnology are not inherently more dangerous than products of other techniques; and that existing regulations can cover them).

Experience Base—Some 46 licenses that have already been granted for small-scale release of veterinary biologics went through the full testing and now qualify for ''large-scale' release. Other projects are still in the research stage (95).

One of the best known small-scale field test cases is that of the genetically engineered rabies vaccine developed by the Wistar Institute, with its corporate partner Rhone-Merieux. This is a Vaccinia virus expression system, with a gene for a protein of the rabies virus, that is intended to stimulate an immune response, but that cannot cause rabies. Provisional approval was given early in 1989 by USDA; the actual distribution of 3,000 ampules of rabies vaccine in an odoriferous bait took place on uninhabited Parmmore Island, Virginia, in the fall of 1990. South Carolina had declined to have an offshore island field test take place within its boundaries.

The owner of the Virginia island, the Nature Conservancy. negotiated long and hard regarding the release. The Wistar Institute had to agree to provide full insurance coverage and indemnification against any lawsuits to the Nature Conservancy. The Conservancy demanded a strong voice in field trial and animal monitoring protocols. Although Wistar researchers assert that any risk from the release is very remote, the apparent ''lack of control (putting bait in the wild and waiting for animals to eat it) certainly helped to arouse concerns. A similar vaccine is being tested widely in Europe, and the Wistar Institute has had discussions regarding additional sites in the mid-Atlantic States (25).

On the basis of satisfactory results from the Virginia field trial and additional data confirming safety in other species, APHIS authorized a second field trial in Sullivan County, Pennsylvania, on June 7, 1991, with little or no adverse public comment, and New Jersey is considering a field trial as well. In contrast. early in APHIS' review of animal biologics, a suit by Jeremy Rifkin's organization, the Foundation for Economic Trends, resulted in a voluntary 2-week suspension of the license issued for the first recombinant-DNA derived category 11 pseudo-

rabies vaccine while APHIS prepared documentation of the assessment conducted during the licensing process.

Large-Scale Release for Veterinary Biologics

Theory-The USDA uses information from early small-scale trials in its subsequent assessment procedure. Biological products progress from physical containment to large-scale use in the field as follows:

1. Movement from stringent containment conditions (level 4) to quarantined field conditions (level 3).
2. Restricted field tests (level 2).
3. Unrestricted geographical distribution on issuance of a license (level 1).

Experience Base—As of October 1, 1991, APHIS had approved field testing and subsequently granted licenses for 39 Category One veterinary biological products. Twenty-six of these were for diagnostic kits; five were for bacterins, and three were for monoclinal antibodies for prophylactic or therapeutic use. The first, a bacterin, was licensed in October 1983; all have been used successfully on a large scale. Seven licenses were granted for category 11 products, all of which were designed to treat pseudorabies in swine. No licenses have yet been granted in category III, but APHIS has received, evaluated, and approved an application to field test a recombinant-DNA derived live rabies vaccine (95).

The following category I and 11 licenses have been issued:

- Salsbury Labs and Norden Labs were the first licensees for bacterins in category for genetically engineered *Escherichia coli* against swine disease.
- Molecular Genetics Inc., received licenses for category 1, therapeutic or prophylactic use, for monoclonal antibodies.
- Among the category 1 diagnostic test kits licensed were kits for equine infectious anemia, avian reovirus antibody, and feline leukemia and feline T-lymphotropic lentivirus.
- At least four companies received category 11 licenses for a modified live virus used as a pseudorabies vaccine.

Authority for Animals

Statutory Authority and Regulatory Policy

The Federal Meat Inspection Act (FMIA) (21 U.S.C. 601 et seq.) and the Poultry Products Inspection Act (PPIA) (21 U.S. C. 451 et. seq.) give responsibility to USDA's Food Safety and Inspection Service (FSIS) for the safety, wholesomeness, and proper labeling of food products made from domestic poultry and livestock. FSIS inspects the organisms and cleaned products intended for use as human food.

Under the slaughter of research animal provision of the FMIA and the PPIA, FSIS has developed regulations stating that no livestock or poultry used in a research investigation is to be slaughtered at an official establishment until sufficient data demonstrate to FSIS that the edible products derived from the research animals are safe for human consumption (9 CFR 309.17 and 381.75). These regulations pertain to the slaughter of transgenic animals as well as animals treated with recombinant DNA-derived products.

Implementation

In the event of a request for slaughtering approval, FSIS would coordinate its review with the agency having jurisdiction over the experimental product (e.g., APHIS—biologics, FDA—drugs, food. and feed additives, EPA—pesticide chemicals.) Usually, data gathered by each individual agency is adequate for FSIS evaluation. Once approved for slaughter, research animals are subject to the same inspection standards as nonresearch animals. If some animals derived through new technology, such as mosaics, chimeras, and some hybrids, differ significantly from currently inspected animals, the FSIS will determine on a case-by-case basis whether the animals are covered under FMIA or PPIA or if the acts need to be amended to require inspection. FSIS also has authority over substances used in processing meat and poultry products; the use must be in compliance with applicable FDA regulations and must be functional, suitable, and kept to the lowest level necessary (I I).

The FSIS has not yet had to test its interpretation or implementation process in a case involving animals modified through biotechnology (1 I).

EPA

EPA has jurisdiction over two broad classes of products (pesticides and ''new' chemicals) under three Federal statutes—the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA): the Food, Drug, and Cosmetic Act (FD&C); and the Toxic Substances Control Act (TSCA). Under the authority of FIFRA, EPA regulates the manufacture, processing, distribution, and use of pesticides and sets tolerance levels for pesticides in food and feed as directed by the Food, Drug, and Cosmetic Act (discussed in the food safety chapter). Under TSCA,

EPA must screen any ‘*new” chemical before it is introduced into commerce to determine whether or not its use presents an unreasonable risk to health or the environment and is not otherwise regulated. This section reviews EPA’s statutory authority under FIFRA and TSCA and discusses its application to the regulation of biotechnology products.

EPA attempts to forge a coordinated and consistent approach to its biotechnology responsibilities under FIFRA and TSCA to the extent possible given the different mandates of the two statutes. Despite these different mandates, both approaches to regulation are concerned with microorganisms having:

- ‘‘new’ characteristics (intergeneric combinations of genes) that are new to the environment in which they will be released;
- potential for adverse effects on other organisms; and
- potential for widespread exposure because they are used in the environment.

Because FIFRA regulations were already applied to microbial pesticides, an interim regulatory policy announced in the Federal Register on small-scale field trials in relation to Experimental Use Permit (EUP) regulations was the only change necessary for the ‘‘new’ biotechnology. However, a set of regulations for microorganisms is needed under TSCA so that EPA can regulate living microorganisms more readily. The agency heretofore has dealt principally with new chemicals, although microorganisms have been included in the TSCA Inventory of Chemical Substances since its establishment. Regulations could be developed by applying the statutory provisions of TSCA and EPA’s current oversight program for new chemicals to microorganisms. The delay in the development of these regulations has been noted with particular concern by the biotechnology community as likely to have caused uncertainty among applicants and would-be applicants for deliberate release.

For assistance in regulating biotechnology, the EPA formed its Biotechnology Science Advisory Committee (BSAC) in 1986 to give peer review of EPA assessments of product submissions, as well as scientific advice on its biotechnology program. Among other responsibilities, the BSAC has been involved in advising on terms for regulations, on benefits and risks of the use of antibiotic-resistance genes as markers in field tests, and on peer reviews of some EPA assessments of field test submissions (67).

Authority of FIFRA

Statutory Authority

As noted above, pesticides, including those produced using biotechnology, are regulated by EPA under the aegis of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). FIFRA was enacted June 25, 1947, “to regulate the marketing of economic poisons and devices” (6 I STAT. 168; 7 USC sec 135c); it has been amended multiple times in the intervening years with major substantive amendments in 1972. 1978, and 1988 and more anticipated in the early 1990s.

The heart of FIFRA is the requirement that all pesticides be registered. EPA must certify that the use of a pesticide does not pose an ‘‘unreasonable adverse effect’ in order to register a pesticide. In deciding whether a pesticide use poses ‘‘any unreasonable risk to man or the environment, EPA must take “into account the economic, social, and environmental costs and benefits of the use of any pesticide. ” EPA must also consider the impact of any regulatory action "on production, prices of agricultural commodities, retail food prices, and otherwise on the agricultural economy. Registration requires the submission by the manufacturer of extensive data on the efficacy and human and environmental effects of the pesticide. EPA uses this data in deciding whether to register the pesticide and whether to impose conditions on its manufacture, processing, distribution, and use.

After registering a pesticide, EPA retains regulatory control via the reregistration, cancellation. and suspension provisions of FIFRA. Section 6 (a) of FIFRA establishes that registrations are canceled after 5 years unless EPA receives a request for a new registration, at which point EPA may request new data about the pesticide and may, on the basis of this new information, alter the conditions of the registration. EPA also has the power to cancel a registration at any time if the agency finds that the pesticide poses an unreasonable adverse effect; however, the cancellation procedure is complex and time-consuming. If the use of a pesticide poses an imminent hazard, EPA may immediately suspend a registration.

Agency Interpretation and Regulatory Policy

EPA’s principal experience base lies in evaluating conventional chemical pesticides where risk issues may differ significantly from those of living organisms. Nonetheless, microbes (e.g., bacteria. viruses, fungi, and protozoa) producing pesticides or pesticidal substances. as well as plants modified to produce substances to control pests, can be interpreted as falling within the statutory

definition of pesticide. EPA's office of Pesticide Programs has built a group and experience in regulation of microbial pesticides since the late 1970s. EPA will register these products it it concludes that the benefits of their use outweigh the risks. More controversy has arisen over whether pest-resistant plants are equivalent to pesticides. since all plants have some pest-resistant characteristics naturally. EPA has never, for instance, regulated plant varieties. such as virus-resistant lines, classically bred to have "pesticidal" properties.

Microorganisms- On October 17, 1984, EPA published in the Federal Register a notice that it would "require notification prior to all small-scale field tests involving certain microbial pesticides in order to determine whether experimental use permits are required. This is in contrast to small-scale field tests of conventional chemical pesticides. An EUP is not required for the latter if under 10 acres of land or 1 acre of water is involved. The difference in policy is based on the premise that the concepts of "small scale" or ''small quantity' arc not applicable to living organisms capable of movement and reproduction. Notifications are required for field tests involving non indigenous microorganisms. microorganisms genetically altered by ''traditional means, such as mutagenesis, and recombinant microorganisms. In the case of most of these notifications. no problem is perceived by EPA and no EUP is required.

In a February 15, 1989, Federal Register notice. EPA announced its intent ion to amend FIFRA regulations to require notice for small-scale releases involving I) microorganisms whose pesticidal properties have been altered by introducing intentionally manipulated genetic material; and 2) microbial pesticides formed by the combination of genetic material from organisms from different genera.

In an attempt to maintain flexibility, EPA is currently considering a mechanism for exempting small-scale field tests of microbial pesticides from the notification requirement as increasing information and experience so justify. Only organisms with higher risk and those that arouse higher levels of public concern would remain the targets of reviews. A draft amendment to the regulations is circulating within EPA that would clarify the scope of organisms requiring notification, emphasizing only those organisms that carry significant possibility of risk or raise high levels of public concern. There has been some support for exempting nonindigenous microorganisms and microorganisms genetically altered through traditional means from notification requirements, expressed in terms of the very absence of comments received on publication of such notification in the post (67, 91).

Plants—In 1987, the EPA Office of Pesticide Programs (OPP) and USDA's Animal and Plant Health Inspection Service (APHIS) agreed to review cooperatively proposals for field tests transgenic plants that fall under the Federal Plant Pest Act. Currently, while tests are at a small scale. on an operational level APHIS takes the lead, with OPP providing comments. Under discussion is the possibility that OPP take the lead when the plants are grown on a large scale for food use. In some cases, the products of large-scale tests might be intended for food or teed USC. Modifications to 40CFR 152.40 CFR 158, and 40 CFR 172 may be needed fo new data requirements and variations on Experiment Use Permits. EPA might regulate field trials of plants with pesticidal properties, or it might set tolerance levels for residues in approved food products.

To gain input as it develops procedures t-or evaluating transgenic plants, EPA conducted a workshop in June. 1990 to discuss scientific issues and seek guidance on the information needed to conduct these evaluations (23). In November of 1990, EPA held a second information gathering conference, this one focusing exclusively on pesticidal transgenic plants. One topic addressed is how to adopt the agency's usual "maximum hazard". testing approach, in which artificially high concentrations of a chemical are used to evaluate the safety of plants that produce a pesticidal chemical in small amounts; if extra supplies of the chemical are generated (in bacteria) for the tests, will this material be identical to the plants chemical, so that the test is valid? Such complexities not withstanding, EPA under FIFRA has a much more focused task—regulating substances designed to harm some living systems—than FDA, which will have to consider the much broader arena of genetically engineered plants as food. (See ch. 10 and 11.)

Other Organisrns-Microorganisms used against other insects, such as nematodes or parasitic wasps, do not fall under the purview of FIFRA. However, the demands of particular isolated cases can elicit FIFRA staff involvement. In one case, parasitic wasps were used to control infestations in certain grain elevators in Texas. The FDA inspector checking for insect parts in the food requested a tolerance level from EPA. EPA could not comply because it had never registered the wasps as a pesticide. After much interagency communication back and forth, EPA developed a memo of exemption. This was the one case to date in which EPA staff has dealt with animal

microorganisms. EPA is not involved, for example, in a case of a pesticidal nematode carrying bacteria because it is seen as a microorganism system. If, however, the bacteria in the system were genetically engineered, OPP would want to take a look at it (91).

Implementation

Basically, EPA reviews a proposed test and decides whether to allow the test, request more information, or require an Experimental Use Permit, for which the target review time is 90 days. Companies are encouraged to hold discussions with FIFRA officials prior to the notification and EUP stages.

Review is conducted on a case-by-case basis by FIFRA staff. A list of data that must be submitted with a notification is available and includes, among other components:

- the identity of the microorganism;
- means and limits of detecting the microorganism in the environment;
- physical, chemical, and biological features influencing the growth and survival of the microorganism;
- information on likely survival in the environment(s) into which the microorganism will be introduced;
- the genetic manipulations involved. in detail;
- data on potential for gene transfer, detailed description of the test program, including monitoring; and
- any additional factual information on possible adverse effects.

Aspects considered by staff include: hazard and exposure, potential problems or issues, important questions needing answers, and likelihood of risk.

Staff positions are then shared for comment with intra-agency workgroups, other Federal agencies if appropriate, State agencies, and, if needed, the BSAC. Although a State-FIFRA Issues Research and Evaluation Group exists, EPA does not yet seem to have tapped or developed an established, extensive system of State-level biotechnology contacts comparable to that of USDA. Public comment is regarded as important; for some proposals, several opportunities have been provided. Notice of all notifications appear in the Federal Register; significant EUP's, including all biotechnology EUP', are placed in the Federal Register as well. Companies are encouraged to inform local communities of upcoming field tests.

If the analysis indicates unreasonable risks are likely, EPA can impose restrictions. Risk management can include constraints on use, disposal, and manufacture, as well as mitigation, monitoring, or other actions. As a way of checking on its evaluations, and adding to its information base for future tests, EPA has worked on the development of monitoring methods that will lead to understanding of the possible fate and dispersal of microorganisms in the environment (67).

Application of FIFRA

Small-Scale Release

Theory—EPA under FIFRA approaches small-scale field trials on a case-by-case basis.

Experience Base—From 1984 up to 1989, the Office of Pesticide Programs (OPP) reviewed 36 submissions (notifications and EUPs) under FIFRA. Of 25 notifications reviewed, 21 were approved with no EUP required, 1 was withdrawn, and an EUP was required for the remaining 3. Of 11 EUPs reviewed, 10 were approved, with a decision on 1 pending (96). Companies making submissions included: AGS, Mycogen, Monsanto, Ecogen, Rohm and Haas, Crop Genetics International, and Sandoz. Universities included the University of California, Montana State University, Cornell, and the University of Arkansas. Nearly half of the tests involved *Bacillus thuringiensis (85).* So-called ''pesticidal plants," transgenic plants that produce pesticidal chemicals, are reviewed in conjunction with USDA-APHIS, with EPA-FIFRA staff providing comments to USDA-APHIS. Tomato plants engineered with *Bacillus thuringiensis* toxin genes and tobacco plants engineered with Tobacco Mosaic Virus coat protein genes are examples. Both have been explored by more than one company. Companies whose applications for transgenic pesticidal plants received informal review by EPA are: Rohm and Haas, Monsanto, Agrigenetics, Sandoz, DuPont, and Agracetus (97).

The first review of an EUP application for a genetically engineered microbial pesticide (a test by Advanced Genetic Sciences, Inc., of the Ice-minus (INA) *Pseudomonas syringae)* took nearly 2 years from receipt of application to the field test. Two lawsuits involving Federal and State courts temporarily stopped the test; many administrative proceedings at the State and local levels caused further delays.

In contrast, a later application on an EUP submitted by Crop Genetics International in December of 1987 was granted in May of 1988, less than one-half year later. The field test was begun in June and data for the test were submitted in application for an extension and ex-

pansion of the EUP. This test involved the insertion of a *Bacillus thuringiensis* toxin gene into a plant endophytic bacteria (67).

OPP considers any microbial pesticides to be biotechnological in the broadest sense; even biochemically based pheromone products are biologically active systems designed to alter the behavior of insects. At least three-quarters of the Office's workload is comprised of nonrecombinant microbial pesticides; recombinant products represent only 1 to 5 percent of the number of notifications received. While numbers of new chemicals to be reviewed have plateaued over the last 5 to 6 years, microbiological/biotechnology products are increasing linearly such that they now comprise approximately one-third of the reviews. Plans exist to add biologically trained staff during the upcoming year (91).

The early stages of the regulatory life cycle of a new microbial pesticide is illustrated by a planned introduction of dead recombinant organisms into the environment. In 1986, Mycogen discussed its killed recombinant bacteria with FIFRA staff who, on receiving requested data proving that the bacteria were in fact dead, told the company that it did not need to submit a notification. In 1988, the company was moving its trials into sites larger than 10 acres, the stage where an EUP was obtained from EPA. In 1989-90, field tests took place on some 5,000 acres per year. In 1991. the company had several products approved for registration as a pesticide (91).

EPA has also approved field trials of live recombinant organisms by Repligen and Sandoz Research Corps. Field trials of recombinant *Bacillus thuringiensis* on soybeans infected with beet army worms were approved for the fall of 1990 at Sandoz's Mississippi station (86). Interest in microbial pesticides is growing among large companies.

Large-Scale Release

Although naturally occurring, classically derived, and killed recombinant products have moved through large-scale testing and commercial registration, no large-scale releases of *liverecombinant* organisms have as yet been approved under FIFRA. However, at least one company has had a series of discussions with EPA staff on testing design.

Authority of TSCA

Statutory Authority

The Toxic Substances Control Act (TSCA) was enacted in 1976 to regulate the manufacture, processing. and use of chemicals that may pose an unreasonable risk to human health or the environment (15 USC section 2601-54) (13, 87). Because Congress intended TSCA to be gap-filling legislation. it gives EPA broad regulatory authority over a range of substances not regulated under other Federal laws. In determining the appropriate type and level of regulation to impose. EPA must ''consider the environmental, economic, and social impact of any action [it] takes or proposes to take" {15 USC sec. 2601 (2)]. As with FIFRA. EPA must carry out a risk benefit analysis before imposing restrictions on the manufacture, processing, or use of any chemical.

TSCA primarily is a mechanism for screening new chemicals. EPA can review new chemicals for unreasonable risk through the mechanism of manufacturers being required to submit a premanufacture notification (PMN) to EPA prior to the manufacture of any new chemical, i.e. , any chemical not included on the EPA inventory of chemical substances (TSCA sec. 5, 40CFR 720.25). Under TSCA. EPA has the authority to limit or prohibit the manufacture, processing, or distribution in commerce of a new chemical substance if it determines that the chemical substance may present an unreasonable risk to health or the environment, or pending the development of sufficient data to assess whether the chemical substance presents an unreasonable risk. The burden is on EPA to establish risk rather than on the manufacturer to establish the absence of risk. If EPA ascertains that a chemical poses an unreasonable risk or that there is insufficient data to determine the effects of the chemical, EPA can require the manufacturer to test for toxic effects. TSCA subsection 8(e) requires that manufacturers and processors maintain records of "significant adverse reactions to health and the environment (40 CFR 717. 12) and requires submiss ion to EPA of any information supporting a conclusion that a chemical or microorganism presents a substantial risk to health or the environment.

Under its authority to limit or prohibit use of new chemicals posing unreasonable health or environmental risks, EPA may establish conditions for the manufacture. processing, packaging, exposure. and labeling of such chemicals or ban them outright. EPA also can issue controls over chemicals through the significant new use (SNU), reporting, and imminent hazard provisions. The SNU provision requires prior notification for a significant new use of a chemical as defined by EPA. The agency then can set conditions, limitations. or prohibitions based on a new intended use of a chemical. Finally, as with many Federal statutes, TSCA has an imminent hazard provision

that enables EPA to take action quickly if a chemical poses a serious risk (15 USC sec. 2606).

Agency Interpretation and Regulatory Policy

1986 Coordinated Framework Policy—EPA primarily uses TSCA section 5, with its requirement for a PMN prior to the manufacture of any new chemicals to deal with products of biotechnology. The Coordinated Framework (51 FR 23302-23393, June 26, 1986) (77), which designated responsibilities for various biotechnology products held by various Federal agencies, included a policy statement by EPA as to how the agency intended to use TSCA for the regulation of biotechnology; the statement described the categories and microorganisms subject to TSCA, review procedures, and types of information to be submitted for risk assessments. At the most fundamental level, living organisms are considered to be chemical substances under TSCA. Basically, EPA views certain intergeneric microorganisms (microorganisms formed by deliberate combinations of genetic material from organisms in different genera) as ''new chemicals' and therefore under its purview. TSCA pertains to microorganisms used in commercial applications *not* regulated under FIFRA, FDCA, and other statutes; these applications include chemical production, waste degradation, conversion of biomass to energy, and other environmental and industrial uses.

While intergeneric microorganisms are subject to review, naturally occurring microorganisms are not considered ''new' and therefore are not subject to the prenotification requirements of section 5(a)(1) of TSCA, although they may be subject to regulation under other sections of TSCA (i. e., the significant new use rules under section 5(a)(2)). Naturally occurring organisms are implicitly considered to be on the TSCA inventory of substances available in commerce. As for all substances subject to TSCA, manufacturers, processors, or distributors of microorganisms must notify EPA immediately if they become aware of new information suggesting risk from the microorganisms to human health or the environment (section 8(e)).

1988–89 ***Draft Proposed Regulations—in*** general, EPA's efforts to develop regulatory policy have not met with success, and 5 years after the appearance of the Coordinated Framework there still exists no firm EPA biotechnology regulations. Two principle efforts towards developing those regulations will be discussed here—the draft proposed regulations of 1988–89, which did not come to be; and, in the next section, the draft proposed regulations of 1991, which are the source of current controversy. Since the issuance of the Coordinated Framework, EPA, in consultation with its Biotechnology Science Advisory Committee, worked in 1988 and 1989 to develop draft TSCA regulations for biotechnology. Under the 1986 Framework policy, small-scale biotech R&D efforts involving field tests of intergenerics were requested to submit a PMN. The 1989 draft regulations under TSCA proposed a new regulatory mechanism, the TSCA Experimental Release Application. This mechanism involved the use of Environmental BioSafety Committees (EBC's), based on the concept of Institutional BioSafety Committees (IBC's) established earlier through the NIH-Recombinant DNA Advisory Committee (RAC).

This draft EPA rule was reviewed by the interagency Biotechnology Science Coordinating Committee (BSCC) at several meetings. Many concerns were reportedly raised, including the scientific basis for the draft regulations. EPA responded to some comments by sister agencies by making some modifications and then sent the draft proposed regulations to the Office of Management and Budget (OMB) for clearance. BSCC requested that OMB hold clearance until BSCC had time to review its interagency; friction ensued (92).

A Request for Comment on Regulatory Approach was published by EPA in the Federal Register on February 15, 1989 (54 Federal Register 7027). Questions raised for comment included: scope of the microorganisms to be subject to EPA's review; scope of EPA's review of R&D field releases of microorganisms into the environment; breadth of definition of ''commercial purposes' by which EPA would have authority under TSCA in educational and research facilities; definitions of 'release to the environment' and ''contained facility"; and to what extent review was to be performed for EPA by independent expert review groups, such as Environmental BioSafety Committees. The draft regulations did not survive. Rulemaking was delayed until EPA policy and plans for TSCA could incorporate the scope document arrived at by interagency consensus.

1991 ***Draft Proposed Regulations—The*** most recent draft TSCA regulations, integrating some eight specific rules, appeared and were extensively reviewed in 1991. Once EPA has completed the process of responding to the recommendations of the BSAC Subcommittee regarding this draft, the regulations enter the final phase of the Agency's internal review process.

Under EPA's portion of the 1986 Framework Policy, reporting by persons intending to introduce intergeneric

microorganisms into the environment for R&L) purposes is voluntary. EPA is now proposing that this is no longer voluntary. However, researchers intending to introduce intergeneric microorganisms into the environment for R&D purposes would at least have the option of filing a TSCA Experimental Release Application. or TERA, as an exemption from a full 90-day notification that would otherwise be required from commercially oriented applicants. The expedited TERA review would generally be completed in 60 days. The extent of the reporting of environmental R&D required will depend on the eventual selection of an interpretation of the statutory phrase ''commercial purposes. In addition, EPA proposes to exempt some categories of microorganisms when introduced into the environment for R&D purposes (30). The proposed approach is different from the agency's treatment of chemicals, for which review of small-scale R&D activities is not required, presumably because, unlike microorganisms, chemicals cannot reproduce, disseminate, and transfer genetic material.

In 1986, EPA had stated that it would try to derive exemptions for some organisms used in contained facilities: in the current draft, some organisms in contained facilities are exempted from review and only a short review is required for specified lists of industry's "workhorses, such as *Bacillus subtilis.* The list is expected to grow with experience.

The agency views the new document as following directly from the coordinating principles and scientific rationale of the ''scope document' published by the Office of Science and Technology in 1990 as proposed "Principles for Federal Oversight of Biotechnology: Planned Introduction in the Environment of Organisms with Modified Hereditary Traits' [55 Fed. Reg. 31, 120 (1990)] (discussed later). EPA has stated that it will subject to regulatory scrutiny only those "new" organisms that seem likely to present risks. Definitions of "new*' and "risk" are subjects of debate. Some view the 199 I draft-proposed regulations as inconsistent with the OSTP draft's risk-based philosophy. The TSCA 1991 draft proposal effectively singles out recombinant-DNA modified microorganisms for oversight. by exempting other categories such as classical transformation systems (e. g., conjugation or chemical mutagenesis). or rearrangements, deletions, or amplifications of genetic material by recombinant techniques. These exclusions are based on EPA's view that such things could—and do—occur naturally and are thus not . 'new. in contrast to recombinations formed with genes from different genera.

EPA is proposing three alternative interpretations of ''commercial purposes'" in its current draft rule: it may draw a very big net. The first involves selection of commercial indicators that would govern whether a particular field trial would be subject to oversight. The second would apply commercial indicators to R&D conducted in laboratories and greenhouses, for example, and would consider any environmental field release as commercial. and thus subject to screening. The third would permit researchers to rebut the presumption that a field trial was for commercial purposes by showing a lack of commercial intent.

Having potentially drawn so many activities into its ''commercial" net, TSCA would defer to whatever agency would most sensibly handle that activity. TSCA's own coverage might not increase to a great extent. Academic laboratories may well fall under the scope of this ''con~-mercial purpose' if, as is so often the case today. they have some form of a relationship with a company or perhaps even if their home institutions have dealings with industry—as most universities do. Another point of controversy of the proposed draft is its attempt to institutionalize good laboratory procedure and record keeping even in academic laboratories, which previously have not been considered under its jurisdiction (21).

The outcome and the acceptability of the draft are not yet known. It contains controversial points and, 5 years after the appearance of the Coordinated Framework, there exists no track record for quick finalization of EPA biotechnology regulations.

Implementation[3]

EPA currently requests industry to comply voluntarily with the PMN (remanufacture notice) requirements for commercial R&D involving field test releases with intergeneric microorganisms. (Commercial-scale releases are subject to mandatory reporting requirements.) Because the standard TSCA PMN form is not applicable to microbial products, the Program Development Branch of the Chemical Control Division prepared a document, "Points to Consider in the Preparation and Submission of TSCA Premanufacture Notices (PMNs) for Microorganisms, ' in 1990. The document is intended to give guidance for contained system (fermentation) PMNs and

[3] **Note - the preceding section, "Agency Interpretation** and **Regulatory Policy** ." discusses development of **EPA policy,** which **includes proposed implementation. This section examines** *currently practiced* **implementation.**

environmental release PMNs. It specifies points of desired information, including: description of recipient and donor microorganisms, construction of the PMN microorganisms, characteristics of the PMN microorganisms, production process, worker and consumer exposure, environmental behavior of the PMN strain, and environmental release protocols.

Manufacturers or importers of intergeneric microorganisms in and for commerce are required under TSCA section 5(a)(1) to submit a PMN at least 90 days prior to manufacture or import. Communication with a Program Manager in the Program Development Branch, Chemical Control Division, and EPA's Office of Toxic Substance is recommended prior to submission of a PMN. Submitters are encouraged to minimize information withheld as confidential; however, two versions, one with and one without CBI, can be submitted. Companies must now pay a fee of $2,500 for each PMN or consolidated PMN submitted; small businesses must remit $100 per PMN. The EPA publishes a notice on each PMN submission in the Federal Register (17).

Review of PMN's is conducted on a case-by-case basis, and can involve both EPA scientists and outside scientific experts. Following submission of the PMN, EPA has 90 days to make a determination as to if and how to regulate. During this time a scientifically based hazard assessment and an exposure assessment are conducted. (See ch. 8 and U.S. EPA (1987) Toxic **Substances Discussion of Premanufacture** Testing Policy and Technical Issues; Request for Comment. Federal Register 44, 16243-44).

Among the items of information reviewed are:

- the identity and characteristics of the source organism,
- the methods and genetic material used to manipulate the source organisms,
- the nature of any new traits or functions,
- purpose and intended effect of application or release,
- characteristics of the site of application,
- method and numbers involved in application,
- containment and mitigation methods,
- monitoring procedures, and
- data on environmental fate and effects (10).

If EPA determines during the 90-day period that a new chemical substance may present an unreasonable risk to health or the environment, EPA can prohibit or regulate the substance; if it does not do so, the submitter may proceed. An extension to a 180-day review period can occur, for good cause. Other agencies may be asked for comment, and appropriate State regulatory agencies are contacted. Visits to test sites may occur. The BSAC may review submissions and EPA evaluations. Public comment is viewed as important (67).

Application of TSCA

Small-Scale Research

Theory—EPA approaches small-scale field trials on a case-by-case basis. Unlike commercial research involving chemicals, under the 1991 draft of proposed regulations, recombinant DNA small-scale field tests will receive no automatic exemption from the PMN requirement, although an alternative application process (the TERA) may be used.

Experience Base— Since 1986, EPA's Office of Toxic Substances (OTS) has reviewed 20 premanufacture notices (PMNs) for release, with the most recent review completed in April, 1990 (18). It has been speculated that the absence of notices over the last year may reflect an economic climate unfavorable to commercial development of environmental uses of microorganisms (economic climate seems not to have affected plant submissions); uncertainty as to EPA's regulatory role; or the evolution of the science itself. It may be that biotechnology is to some extent moving away from deliberate release of microorganisms; plants may be easier to manipulate than previously thought. Some suggest that the lack of notices received under TSCA simply reflects the fact that no company is now actively developing rhizobia or other microorganisms subject to TSCA. Bioremediation, the commercial use of microorganisms to degrade toxic waste, will probably not significantly utilize genetic engineering in the near future. It has been suggested, however, that this particular delay may be related not simply to technical reasons but also to uncertainty about regulatory interpretations.

The first biotechnology application under TSCA was filed by Biotechnica in February 1987. The application was to field test, in Wisconsin, genetically engineered strains of *Rhizobium meliloti* to see if these increased alfalfa yields through nitrogen fixation.

A Subcommittee of the Biotechnology Science Advisory Committee reviewed the field test protocols and recommended that Biotechnica provide a fuller description of the experimental methods being employed at the site in terms of plot design and monitoring of the organisms after release into the field plot. After consideration

of BSAC suggestions and other public comments, Biotechnica obtained EPA approval to conduct the field test in spring of 1988.

Another early submission was a request in June of 1987 from Monsanto to field test a fluorescent microorganism genetically engineered to be more easily distinguished from other soil microorganisms under laboratory conditions. EPA completed its review in October of 1987. The field trial was held and it demonstrated the usefulness of the gene as a marker for monitoring. Monitoring of the field trials demonstrated that the organism colonized roots; that the population continued to decline; and that migration was limited (67).

With the exception of Monsanto's field trial, all other environmental use submissions under TSCA have been from Biotechnica. Biotechnica's tests have involved microorganisms genetically modified for improved detection in the environment (antibiotic resistance) and for enhanced nitrogen fixation resulting in potential yield increases (18).

Commercial-Scale Release

Commercial-scale release of genetically modified microorganisms has not yet occurred. EPA might be expected to follow the same case-by-case pattern for commercial-scale release as it has for small-scale release research. As a matter of interest, there have been commercial-scale uses of genetically modified microorganisms in contained systems. Reviews have been completed on 10 PMNs involving the commercial-scale use of intergeneric microorganisms in contained fermentation systems for the production of microbial enzymes.

OTHER AGENCIES

National Institutes of Health (NIH)

The RAC, the Recombinant DNA Advisory Committee at NIH, wrote the now-classic Guidelines for research in recombinant DNA at federally funded institutions and has reviewed cases for compliance with the guidelines. The original Guidelines, issued in 1976, counted deliberate release as one of five classes of experiments ''not to be initiated at the present time"; in the Guideline revisions of 1978, ''deliberate release into the environment of any organism containing recombinant DNA" was prohibited, but provisions were made for waivers through the RAC and NIH; in 1982 revisions, such ''prohibitions" became ''experiments that require RAC review and NIH and IBC approval before initiation' (66).

"Deliberate release" was listed as one of the triggers for RAC review (May 7, 1986, Federal Register, vol. 5 1(88), p. 16960). In fact, however, the RAC has not reviewed any cases since 1987. Since then, EPA and USDA have interpreted their authority to have purview over the vast majority of experiments involving deliberate release. RAC's acquiescence to this allocation of oversight is made clear in its ''Talbot Amendment, stating that once approvals or other clearances have been obtained from an agency other than NIH, the experiment may proceed (Aug. 24, 1987, Federal Register 52(163), p. 31, 849). In addition, the RAC at its February 4, 1991 meeting, voted to consider deleting planned environmental deliberate release as one of the triggers for its involvement in biotechnology regulation. After duly publishing notice and receiving public input, the RAC met on May 31, 1991 and voted to relinquish this overview. The decision now stands before the Director of NIH. NIH funds very few scientists involved in deliberate release; it also lacks qualified staff to conduct EA's. The RAC, however, intends to maintain its overview of work with transgenic plants and animals *inside* laboratories, animal rooms, and greenhouses. RAC's relinquishing of national overview does not preclude local Institutional Biosafety Committees (IBCs) from considering planned introductions or from bringing up problems to the RAC (108).

Food and Drug Administration (FDA)

Because FDA's authority is over the final food product in interstate commerce. it does not regulate research and therefore is not involved currently in the environmental issues concerning deliberate release research. Exceptions are its jurisdiction over live attenuated vaccines and feed additives including live microorganisms. However, if FDA gives some form of approval for the commercial use of transgenic plants for food, it may have to evaluate the potential environmental consequences of that approval, under the National Environmental Policy Act (NEPA). If a company asked FDA to affirm GRAS (Generally Recognized as Safe) status for a food or to state that a particular variety of plant is acceptable as a source for food, FDA would likely have to assess the environmental consequences of the field use of the plant as part of its evaluation of the food product. An FDA ''advisory opinion, however, might not be a major Federal action requiring an environmental assessment.

In its reviews, the agency in the past has limited its environmental assessment to the manufacture and use of the petitioned-for substance. It typically has not reviewed the environmental consequences of the original produc-

tion or development of the materials used at the manufacturing site. In the case of agricultural commodities, however. the plant itself might be viewed as analogous to the manufacturing facility.

If USDA has evaluated the environmental consequences of the field use of the plant, FDA should be able to make use of that information in its own evaluation. It is also possible, although not necessarily likely, that FDA may be able to exclude categorically from its own environmental review those plants that have been reviewed by USDA for commercial use (24).

STATE AND LOCAL GOVERNMENT

Spectrum of State Approaches to Regulation

Significant concern has been expressed regarding the involvement of State governments in the regulation of biotechnology. In addition to coordination with Federal agencies. discussed in a later section. a significant question is the degree to which States should take on independent review authority. On the one hand, State governments may be argued to be "closer to" the people that they are safeguarding and therefore regarded as particularly able or trustworthy as regulators. On the other hand, duplication of Federal regulatory requirements could prove to be an untenable burden on companies. Excessive. idiosyncratic requirements at the State level also might inhibit industrial development. Furthermore, a patchwork of varying State regulatory regimes across the Nation could lead to significant uncertainty on the part of industry, a shopping around for receptive States, or a simple unwillingness to move into product lines related to biotechnology. Compliance with different standards in different States could be a costly problem for industry.

State legislation relevant to biotechnology in 1990 included 19 bills spread among 13 States. These fall in the areas of DNA testing (9). bST (4). R&D and economic development (3), deliberate release (l), general regulations (I). and other (I). In the same year, some 48 bills in 18 States were introduced but not enacted. These referred to bST (20), DNA testing (I l), R&D) and economic development (10), deliberate release (3), general regulations (2), and other (2).

Over the past several years, the nine States of Florida. Hawaii. Illinois, Maine. Minnesota. New York. North Carolina, Oklahoma, and Wisconsin have enacted statutes pertaining directly to field testing of genetically modified organisms. with Maine and New York simply creating advisory committees to study issues. In 1991, West Virginia amended its plant pest act to pertain specifically to biotechnology. Many State statutes simply require notification of field test applications to particular State agencies that are to cooperate with the Federal process. Only North Carolina and Minnesota require additional permits. Policy stances taken by various States fall into a broad spectrum. from no or very little administrative or legislative activity (approximately half the States) to moderate activity to, in a few cases, initiation of new regulatory procedures (16). Case study illustrations of this range of activity follow.

North Carolina

In June 1988 the North Carolina Department of Agriculture and the North Carolina Biotechnology Center formed an Advisory Committee to determine whether or not any State regulation was needed and, if so, to develop a suitable regulatory framework. The 27-member Committee included university and private-sector researchers, administrators, business executives, lawyers. and farmers and representatives of government, public interest, and other groups. The committee's recommended regulation was passed by the North Carolina General Assembly in August of 1989 as the Genetically Engineered Organisms Act. Funds were appropriated for a staff biotechnologist in the North Carolina Department of Agriculture to administer the law, which requires a permit (either general or limited) for environmental release and for the sale of genetically engineered organisms, with public notice given (8, *16).*

Minnesota

In response to public suggestions in 1987 for rule changes to the Minnesota environmental review regulations, the Minnesota Environmental Quality Board formed a working group on environmental release, which recommended that the EQB should be a coordinating body for genetic engineering. A Task Force was formed, and its report was implemented by legislation in 1989. A permit is required for environmental release of genetically engineered organisms. The EQB is charged with establishing an advisory committee. reviewing proposals, and adapting rules for an environmental work sheet and for a permit for releases (8, 16). Recently, issuance of resultant proposed regulations under the EQB law have caused much controversy. A process for permitting, including an environmental assessment worksheet, would be required for each release of a genetically engineered organism (defined fairly broadly.) Legislation in 1991 created areas of specific permit authority for the Minnesota Agriculture

Department (transgenic plants; genetically engineered and experimental pesticides; and genetically engineered fertilizers. soil, or plant amendments). EQB regulations would therefore cover transgenic animals and nonagricultural engineered microorganisms. Both agencies, however, must follow the same specific procedures in proposing environmental assessments (34).

California

The well-publicized field tests of ice-minus bacteria in Monterey County in 1983-84 (see U.S. Congress, OTA. 1988 for the full case study) (102) led to a recommendation that California clarify its biotechnology regulations. Thus, an Executive Order in 1985 established the California Interagency Task Force on Biotechnology. The Task Force systematically identified, evaluated, and communicated the level of regulatory control already pertaining to various biotechnology activities in California. The first product was a handbook, ''Biotechnology-California Permits and Regulations," published in 1986, with at least 3,000 copies distributed by the summer of 1989. The chief finding was that the current regulations were quite complete in their coverage of biotechnology. Four permit procedures were enhanced to provide for increased input from the public (8, 16).

New Jersey

Stimulated by the repeated introduction (without enactment) of a State legislative bill that would have regulated environmental release, and by the enactment of several local ordinances for such regulation, the New Jersey Department of Environmental Protection developed a white paper on recommendations for the development of State policy on biotechnology. Following informal discussions among agency representatives, an Interagency Committee on Biotechnology was appointed by Departmental Commissioners in the fall of 1989. with university advisors. The committee is evaluating:

- the effectiveness of State laws to regulate biotechnology,
- coordination with Federal agencies,
- the needs of industry in complying with regulations,
- other States' policies,
- the need for biotechnology education, and
- appropriate roles of the State and its agencies.

The first priority is evaluation of New Jersey statutes and coordination with Federal agencies, with the objective of compiling a California-like handbook (8).

Inter-State Gatherings and Consensuses of State Regulators

In recognition of the importance of State regulatory agency officials as part of the full system of regulation. the USDA hosted conferences in 1989. 1990. and 199 I on "Federal and State Regulation of Biotechnology ." Emphasis was placed on clear communication from Federal agency representatives to State agency representatives about the details of the implementation of Federal biotechnology regulations. The 1990 meeting attracted some 130 people. the great majority from State agencies. University, private-sector. and environmentalist representatives attended as well. The third meeting, in 1991. concentrated on the issues of large-scale commercial release.

In recognition of the varying degrees of unease felt by State regulators having to come to grips with biotechnology, a special workshop for State agencies, "State Oversight of Biotechnology, " was held in conjunction with the second Federal conference, sponsored by the University of California Systemwide Biotechnology. Research and Education Program and the New Jersey Department of Environmental Protection. Case histories of the development of various State policies were shared. Brainstorming seminars led to a consensus set of recommendations for State regulatory officials. The resulting document, "Guidance for State Governments on Oversight of Biotechnology, " included the following "Points to Consider" for States considering how to handle biotechnology oversight:

1. evaluation of the existing (Federal and State) oversight framework for biotechnology;
2. organization of a task force to include representatives from multiple agencies, industry, academic and public interest groups; and
3. activities of the task force, which should include identifying and reviewing existing State statutes and Federal agency roles; recommending needed actions. if any; delineating clear pathways for applicants to follow; working with local governments; and communicating with and involving the public (39, 59).

In 1991, a follow-up workshop emphasized specific points at which coordination between State and Federal agencies could be fine-tuned.

Spectrum of Local Approaches to Regulation

The first local response to biotechnology occurred in Cambridge. Massachusetts. in the ordinances passed in

1977. Concerns over genetic engineering research in university laboratories led to sometimes heated hearings and local regulations. Some years later, an equilibrium seems to have been reached between town and gown. Some companies find the existence of known local regulations to be positive, although others find them problematic and subject to change with newly elected local politicians.

Such an open clash has been fairly unusual, although in one 1989 case the city of Burlington, Vermont and the University of Vermont clashed over the construction of a building to house much of the university's molecular biotechnology research. The city demanded input into, if not the approval of, experiments to be conducted in a new building. The University refused, and the press attacked the University's stance (6). In March of 1991, a Memorandum of Understanding between the city and the University called for the establishment of a task force to discuss plans together. Like Cambridge, Burlington was not particularly concerned with deliberate release.

In New Jersey, on the other hand, initial local concerns focused on perceived risks associated with deliberate release of genetically engineered organisms. When State-level legislation was not enacted, concerned politicians provided to municipal governments model ordinances to restrict the environmental release of genetically engineered microorganisms. By early 1990, six municipalities had adopted such ordinances. Other municipalities debated such ordinances, but decided against enactment, in part because pertinent expertise was recognized as lacking at the local level (41).

To forestall negative public reactions, the AgBiotech Center of Rutgers University in New Jersey began working with the local community from the earliest moment. They formed a Citizens' Advisory Committee to provide input and air public concerns over its planned field-trial facility for genetically engineered plants. Local planning boards, a homeowner's association, farmers, and agricultural organizations appointed members to the committee. The committee reviews plans for the facility and applications for field trials therein. The committee also is charged with communicating information to the public (88).

INTERNATIONAL REGULATORY CLIMATE

Biotechnology, as a scientific endeavor and an industrial activity, is international in scope. Those concerned with U.S. economic competitiveness or with the global environment have reason to be interested in the degree to which deliberate release regulations are internationally consistent and coordinated. A brief sketch of regulatory approaches in several countries follows.

Europe

Status of Regulations, EC 1992

European Community (EC) directives were passed in April of 1990 concerning contained use and deliberate release of genetically modified organisms. Member States were supposed to draft national laws by October, 1991, in alignment with these ''minimum standard' directives. Each State can, and some may well, add more restrictive measures; different member States will achieve different balances regarding restrictiveness of regulations. Pressure groups such as the Greens in Germany, for example, will attempt to counteract the voices of industry concerned with economic competitiveness. Despite the potential for some country-to-country variation in regulatory rigor, the directives are meant to provide more of a ' 'bottom line" consistency among States in terms of protecting the environment than was present in the past.

According to the EC Directive on the Deliberate Release of Genetically Modified Microorganisms, No. 90/220/EEC, releases are permitted only in countries with relevant national approval procedures. The EC hopes for an EC-wide approval procedure for releases of commercial products. This would allow free distribution of products throughout the EC. Deliberate releases will be evaluated and approved or disapproved on a case-by-case basis; hence, there may be room for flexibility in and evolution of regulations. Environmental impact assessments and consent by competent authorities are prerequisites of release.

Different stages in establishing a basis for national decision making have been reached by different EC countries. Approximately one-half of the member States passed implementing legislation by the October 1991 deadline. In the United Kingdom (UK), a biotechnology regulatory framework is part of an introduced Environmental Protection Bill that is intended to form the basis of future detailed regulations. In Germany, the Gene Law was enacted in July 1990. Under pressure from some of its largest industries, Denmark retracted its extremely stringent 1986 law; deliberations as to implementation of EC directives are ongoing. In France, procedures are straightforward and nonburdensome; over 50 field trials have taken place. In the Netherlands, permits for field trials are granted by the Ministry of the Environment

(105). In France, some 67 "uncontained experiments" took place between 1987 and 1990 (12).

Some analyze EC directives with a positive spirit and view the goal of developing a coordinated science-based approach to regulation as helpful to biotechnology in the long run. Science-based regulation, even if it varies among member countries, may well be preferable to idiosyncratic applications of disparate laws already on the books in different countries (47).

In any event, it is not yet clear what balances will be achieved by diverse countries weighing such factors as environmentalist pressures, industry lobbying, scientific findings, and competitiveness concerns. The foundation is laid for commonality, but the likelihood is that different countries will find their own paths. True homogenization is not likely to be achieved by "Europe 1992. The loathing that industry feels for regulatory uncertainty might give the United States at least a transient competitive advantage over at least some countries if regulatory uncertainty here is minimized.

The Fourth Hurdle

The "fourth hurdle" causing real worry among biotechnology advocates refers to a fourth criterion for European regulations of biotechnology. This fourth criterion would be the inclusion of socioeconomic values in the approval process. The **usual three technically based hurdles** for regulations generally are safety, quality, and efficacy (15). The fourth hurdle is controversial, and of great concern even to U.S. industry. Perhaps discussion of this hurdle has peaked already, and it may be declining in importance. However, observers believe that interest could intensify again at any moment. An attempt based on socioeconomic values to ban veterinary growth hormones was voted down late in 1990, suggesting that institutionalization of such values may be unlikely (47).

Harmonization

Despite differences among member states and among EC directorates, European countries and the United States are making good-faith efforts to harmonize regulations. Enlightened self-interest regarding economic competitiveness doubtless plays a role.

Several forces for harmonization include: The Organization for Economic Cooperation and Development (OECD). the Office of International Epizootics (OIE), United Nations Agencies (UN), The World Bank, and bilateral discussions with the European Commission (EC). The OECD, which includes 25 industrialized countries, many but not all of which are European, has several projects related to regulation of biotechnology, including:

- Good Development Practices;
- Guidance for the Design of Small-Scale Field Research With Genetically Modified Plants and Micro-Organisms;
- Good Industrial Large-Scale Practices:
- Monitoring of Genetically Modified Organisms Introduced into the Environment: Findings and Suggestions;
- Performance Evaluations for Plant Cultivar Development; and
- Food Safety.

OIE discussions focus on development of internationally equivalent. appropriate standards for evaluation of veterinary biological products derived through biotechnology. Within the EC, bilateral discussions have occurred through the U.S./EC Bilateral Discussions on the Environment, the High-Tech Group, and the Task Force on Biotechnology Research (57).

Perhaps the most compelling example of harmonization is the development of a common document on biotechnology safety by the 23 member countries (including many European countries, as well as the United States. Canada. and Japan) of the OECD. First published in-house as "Good Developmental Practices (GDP) for Small-Scale Field Research, " it was reworked and released f-or public comment in 1990. GDP outlines scientific principles and conditions for proposal review and also gives guidance to researchers designing small-scale field tests of plants and microorganisms. The document may be augmented by another paper(s) as more data are compiled: the basic approach is aligned with the principles advocated in the 1989 National Academy of Sciences report on safety in field testing (73). Acceptance of this document by 23 countries has been a significant step toward international harmonization of biotechnology field-trial regulations. The fact that the United States was the lead country in developing the document ensures good harmonization with U.S. regulations: this. in turn, should facilitate international trade (55).

Currently, the United States is the designated lead for OECD in drafting an OECD discussion paper on scientific issues associated with performance trials of plant cultivars. A principal objective of this endeavor is to enable policy bodies to make recommendations and decisions based on sound science when they consider large-scale plantings of new agricultural crops. including those developed with new biotechnology techniques (24). This represents a stage beyond the small-scale research cov-

ered by GDP as performance trials involve more plants and there may be no means of ensuring that plants remain confined to experimental sites. Performance trials, however, still qualify as R&D; issues associated with commercialization of plant crops are not directly addressed in this OECD paper.

Canada

Status of Regulations

Following the lead of a Federal Government task force in 1980, Canada implemented a national biotechnology strategy in 1983 and established the Interdepartmental Committee on Biotechnology in 1985. The committee began with the premises that the product rather than the process would be regulated, building on current legislation. Additional concerns could be addressed with guidelines. Canadian regulations would harmonize with those of other countries wherever possible and practicable. A biotechnology users' guide to Federal regulations has been updated recently, assisting applicants with identification of appropriate agencies, contact people, and procedure. In 1987, an ad-hoc committee was formed on environmental release. Agriculture Canada, dealing with organisms used in agriculture, and Environment Canada, along with Health and Welfare Canada, dealing with microorganisms used for nonagricultural uses, are the chief players in the regulatory arena (14).

Currently, regulatory bodies and others in Canada are considering a draft of Proposed Notification Regulations for Biotechnology Products under the Canadian Environmental Protection Act. Developed by Environment Canada and Health and Welfare Canada. notification requirements will eventually become regulations under the new substances provisions of the Canadian Environmental Protection Act (CEPA) and will apply to new biotechnology products manufactured in or imported to Canada. Notification and assessment periods as well as information required are defined based on whether the biotechnology product will be used in contained manufacturing or released into the environment. All biotechnology products will be considered new substances under these regulations.

Environment Canada is currently in the process of developing a Domestic Substances List for those biotechnology products in commercial use in Canada between 1984 and 1986. Once a microorganism is added to this list, no further notification is required by a user if the product is used for the purpose specified in the list.

Guidelines are being prepared to assist those needing to submit notifications for this list. For release into the environment, notification would be required prior to importation. commercial manufacture, small-scale field trials, or large-scale field trials. Currently, information required for a field trial would include: objectives, site details, experimental design, site supervision, introduction protocols, containment procedures, monitoring procedures, termination procedures, and mitigation procedures. In the interim, while the proposed regulations are being developed, notification to Environment Canada is recommended for those with intent to manufacture or import into Canada biotechnology products (80).

Harmonization

Probably the closest working international relationship in the area of biotechnology regulation exists between the United States and Canada, which may not be surprising given their geographical proximity and free trade agreement. EPA officials have met with representatives of Environment Canada and have had informal contact with other relevant Canadian agencies. USDA officials have met with Agriculture Canada officials yearly for 4 years and communicated between meetings on rationale, procedure, and so on. U.S. companies can do field tests in Canada; requests that U.S. officials accept Canadian field test data are expected in the near future. Review systems similar to the U.S. biotechnology permitting system have been established by Canada, taking into account the basic principles on the safety of field testing shared by all OECD countries (60).

Japan

In general terms, Japan's regulation of biotechnology is in line with international standards. Research guidelines are based on the early NIH guidelines, and industry guidelines are consistent with OECD. The Ministry of Agriculture, Forestry, and Fisheries (MAFF) issued the first regulations on environmental release of plants in the summer of 1989 (103). Government guidelines emphasize a step-by-step approach to field tests and a case-by-case basis for approval (94). USDA has worked with MAFF on how to conduct reviews and in a consultative group on monitoring. Japan's environmental directorate is looking at microbiological field releases. One field test has been approved to date in Japan; Japanese companies are requesting field trials in Mexico (58).

Recognition of the importance of facilitating field trials is growing in Japan. In the second half of 1990, for example, Japan's MAFF announced its intention of or-

ganizing an incorporated association of over 100 Japanese biotechnology-related companies. In addition to promoting biotechnology in relevant industries. the Society for Techno-innovation of Agriculture, Forestry, and Fisheries (STAFF) is expected to be involved in promoting and authorizing field trials of genetically modified organisms (45). In addition, Japan's first isolated. open-air field site for transgenic plants has been constructed in Tsukuba, Ibaraki Prefecture, by the National Institute of Agro-Environmental Science (NIAES). NIAES scientists plan to test environmental effects of tomatoes engineered to resist the tobacco mosaic virus.

Developing Countries

In general. developing countries have neither biotechnology regulations nor focused biotechnology staff in their regulatory agencies. One relatively unusual example of activity is the recent formtaion of the Genetic Engineering Approval Committee in India. The group regulates the production and release of genetically engineered organisms and potentially harmful microorganisms (76). A variety of efforts from the developed countries, some based on differing premises, are being made to include developing countries in current regulatory approaches.

The early stages of harmonization may take place quite naturally in developing countries that have some serious interest in biotechnology. Such countries tend to send representatives to the United States to learn about approaches taken here. APHIS-BEEP for instance. has exchanged information with China, India, Mexico. Costa Rica. Brazil, Argentina, Chile, Nigeria. Kenya, Zimbabwe, Thailand. and the Philippines on regulatory philosophy, mechanisrms by which that philosophy is implemented, and ways to handle risk assessment and risk management. USDA has held a variety of conferences on related topics, which are well attended by international representatives.

Various U. N. agencies are exploring different avenues through which to assist technology transfer of biotechnology to developing countries while safeguarding environmental and human health. The U. N. Industrial Development Organization (UNIDO) has developed a voluntary code of conduct to provide guidance for introducing biotechnology products into developing countries. The World Bank has hired a biotechnology advisor to consider biotechnology issues with the Consultative Group on International Agricultural Research (CGIAR). although most of the 18 CGIAR centers are not yet close to field trials. The National Research Council has published a panel report on "Plant Biotechnology Research for Developing Countries. * Some developing world observers question the appropriateness of automatic wholesale adoption of stringent regulations by developing countries (42).

POLICY ISSUES

Jurisdiction and Coordination

Mechanisms of Coordination at the Federal Level

The 1986 Coordinated Framework, described earlier, was a crucial step in establishing and clarifying jurisdictional authorities for a new technology with diverse applications. To further clarity jurisdiction as biotechnology matured toward products, and to help Federal agencies formulate regulations and guidelines based on existing statutory authority, the Biotechnology Science Coordinating Committee (BSCC) was established by the Office of Science and Technology Policy (OSTP). (50FR 47174-47195, November 14. 1985). BSCC was charged "to monitor the changing scene of biotechnology and serve as a means of identifying potential gaps in regulation in a timely fashion, making appropriate recommendations for either administrative or legislative actions.

Until recently, the BSCC provided a forum for senior policy officials from USDA, EPA, FDA. NIH. and NSF as they attempted to coordinate policy. promote consistency in review procedures, and identify key issues. One outcome of this forum was the interagency funding of the 1989 National Academy of Science (NAS) report, ''Field Testing of Genetically Modified organisms: A Framework for Decision-Making." The BSCC also has helped to resolve jurisdictional conundrums, such as whether EPA or USDA is the lead agency in cases of dual jurisdiction. Despite such positive contributions, however, the BSCC had difficulties achieving consensus on important issues such as risk assessment and management, levels of oversight appropriate for certain organisms. definition o! deliberate release, and coherent standards for oversight (11). These difficulties arose in part because different agencies have different statutory mandates and built-in approaches to regultaion. BSCC also was criticized for its ''closed-door' deliberations and for ''rneddiling" in regulatory agency affairs. Nonetheless. the committee helped initiate formulation of broad principles for regulation (27).

In the absence of agreement within the BSCC, Dr. Allen Bromley. director of the Office Of Science and

Technology Policy, decided that the identification of organisms subject to Federal oversight ''had policy implications beyond the jurisdiction of the BSCC" [55 Fed Reg. 31,120 (1990)] and the issues should be addressed by the appropriate policy body—the President's Council on Competitiveness. Moved under the aegis of the Working Group on Biotechnologyof the Council on July 31, 1990, a "scope document" pertaining to initial releases of biotechnology-derived organisms into the environment was published for public review and comment [55 FR 147, 31118 (1990)] by the Office of Science and Technology Policy. The document, ''Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, ' proposed principles for ensuring the safety of planned introductions, while still not unnecessarily inhibiting the process. Certainly, interagency disagreement has existed. It has been said, however, that the extent of collaboration on biotechnology issues among Federal agencies that took place in the drafting of the Principles is unprecedented (61).

The scope document expands on the Coordinated Framework; its criteria for regulatory oversight are risk-based, with the objective of differentiating between organisms that do and do not require oversight at various levels of jurisdiction. Federal agencies may implement the criteria in their own ways as they categorize organisms according to the risks associated with environmental release and thus can be excluded or exempted from oversight. Some introductions may be considered similar to preceding, safe introductions; for others, risk information or current regulations make additional Federal oversight unnecessary. On the other hand, unfamiliar organisms or organisms that might present a risk not yet assessed would be subject to an assessment (62).

The scope document considered all organisms with deliberately modified hereditary traits as potentially subject to oversight, regardless of the techniques used to produce them. However, exclusions from such oversight should be granted to introductions posing no risk. Examples include: plants and animals produced through natural reproduction or breeding and microorganisms modified by chemical or physical mutagenesis or the transfer of nucleic acids through physiological processes. Such exclusions are based on previous safe experience with products produced with these traditional processes. In addition, organisms produced by other processes, including recombinant DNA techniques, should be exempt from oversight if they pose no greater risk to the target environment than parental strains that are considered safe.

An extremely broad class of organisms potentially is subject to oversight. In this sense, the products of new biotechnology are not singled out as inherently more risky than those resulting from nonmolecular techniques such as plant breeding (55 Fed. Reg. 147,13 1118 (1990). Nonetheless, exclusion from oversight, based as it is on criteria of familiarity, is possible for virtually all methods of modification except those using molecular or rDNA techniques. Just as operationally, regulatory examination to date has been triggered by the process of recombinant DNA, in the near future, at least, other novel techniques are equally likely to draw the attention of regulators, if only because they point to the presence of a novel product. The apparent contradiction between this reality and the scope documents attempt to focus on products, not processes, mirrors the conflicting views of those scientists and industry representatives who maintain that the products of biotechnology pose no unique risks; and those who believe that the novel characteristics of biotechnology products and scientific uncertainty about risks warrants extra caution. The ''product versus process' debate continually resurfaces. An exceedingly fine line divides regulation of a biotechnology *product* and regulation of a process. USDA's approach to the balancing act between process as trigger and product as legitimate focus is to review any implications for the safety of the end-product that might arise from the technique applied. For example, clean characterization of the gene transferred is particularly important if the genetic material is taken from a plant pest, so it is clear that no unwanted genetic information is transferred.

This pragmatic approach should be readily applicable to novel techniques in addition to recombinant DNA itself. Using the safety of the product as the focus for review allows regulators to take into consideration any and indeed all pertinent aspects of any techniques or processes leading to novel products, thereby avoiding gaps in coverage. Algorithms for using risk as the trigger for oversight have been and are being developed (69). Some companies. well advanced in their product development, desire regulations that effectively will end the product v. process debate so that progress can be made in bringing products to market.

On February 27, 1992 the Office of Science and Technology Policy published in the Federal Register (vol. 57, No. 39) its revised scope document, describing policy on "Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products Into the Environment. " A principal change from the draft published earlier is the elimination of a previously controversial exclusion category—exclusion for

conventional technologies. By eliminating this exclusion from oversight, some policy makers believe the new scope document is more consistent with its own premise, i.e., that no special risk is attached to the recombinant DNA modification process. Oversight of conventional and new technologies is, however, left to the regulatory agencies.

Agencies are continuing to craft regulations and guidelines in response to the scope document's policy directives that existing statutes provide sufficient authority for adequate regulation and that regulation should be risk-based. EPA, for example, is crafting its regulations for biotechnology; regulations under TSCA still have not been finalized. USDA's ABRAC guidelines for research have been put out for comment. As biotechnology moves to the commercialization stage, where releases could occur on a large scale, amendments may or may not be needed.

Coordination among agencies is critical, as regulatory policy evolves to avoid redundancy and delays in policymaking. Several interagency bodies will play a coordinating role, including the Office of Management and Budget (OMB), BRS (the research-oriented successor to BSCC), the National Biotechnology Policy Board. and the President's Council on Competitiveness (COC).

The Biotechnology Research Subcommittee (BRS), of the Committee on Life Sciences and Health, is part of the Federal Coordinating Council on Science, Engineering, and Technology (FCCSET). Formed in 1990, the BRS succeeded the BSCC and focuses on issues such as research priorities, needs, and training rather than on policy issues. As an interagency body, the BRS includes the acting heads of the NIH and the FDA, with additional representatives from the State Department and its Agency for International Development. the EPA, USDA. NSF, NASA, Department of Commerce, Department of Defense, Department of Interior, Department of Energy, Office of Management and Budget, and OSTP.

The Administration's final policymaking body for biotechnology, the Council on Competitiveness (COC), includes the Vice President; the President's Science Advisor: White House Council; the Secretaries of HHS, Commerce, Defense, Treasury, Energy, and Agriculture,; the EPA Administrator; the NSF Director; the U.S. Attorney General; and the Chairman of the Council of Economic Advisors. Biotechnology issues will be considered first by the Council's Working Group on Biotechnology.

A significant action in biotechnology by the COC was the publication of its "Report on National Biotechnology Policy' in February, 1991. ***(See*** box 7-C.) The thrust of the report is that biotechnology products essentially are equivalent to products developed through other procedures and that, therefore, the domestic biotechnology industry should not be burdened by ''excessive restrictions. The report also suggested that the COC and its Biotechnology Working Group take the lead in coordinating regulation of products introduced subsequent to the 1986 Coordinated Framework. The Working Group was also charged with coordinating communication among industries; streamlining review procedures; reevaluating regulations as necessary; and dealing with inconsistencies of international. State. and local policies, regulations, and laws (28).

Responses to the COC Report are predictably diverse, ranging from those of environmentalist groups, who still call for special regulatory attention to biotechnology, to industry representatives, who hope that the report will push toward clearly defined regulatory criteria. thus enabling company executives to estimate accurately the time and costs involved in winning approval for testing and marketing biotechnology products (2).

The new National Biotechnology Policy Board, established by the Administration according to the instructions from the Senate Appropriations Committee in its report on the 1989 HHS budget. will play a purely advisory role. Its public members as well as voting governmental members report to the HHS Secretary (100). The Board will review research. nonconfidential privately funded biotechnology activities. and the development of industries and products and make recommendations to the President and Congress (84).

Comparison of USDA and EPA Approaches to Biotechnology Oversight

Each of the two major agencies involved in biotechnology oversight must, under its own specific mandates, attempt to provide technically sound judgments on risk, while expediting regulatory procedures and developing a foundation of experience on which to base future judgments. Types of information used by EPA and USDA to make regulatory judgments include 1) that required for the evaluation of deliberate release applications or notifications, 2) experience base, and 3) application and notification processes. By far, the largest experience base with regard to field trials is that of USDA-APHIS in working with transgenic plants. In terms of products licensed for real-world use, USDA's largest experience base is with category I (animal biologics). While EPA's Office of Pesticide Program deals

Box 7-C—Council on Competitiveness
Report: Four Principles of Regulatory Review

1. Federal Government regulatory oversight should focus on the characteristics and risks of the biotechnology product-not the process by which it is created.
2. For biotechnology products that require review, regulatory review should be designed to minimize regulatory burden while assuring protection of public health and welfare.
3. Regulatory programs should be designed to accommodate the rapid advances in biotechnology. Performance-based standards are, therefore, generally preferred over design standards.
4. In order to create opportunities for the application of innovative new biotechnology products, all regulation in environmental and health areas—whether or not they address biotechnology-shouid use performance standards rather than specifying rigid controls or specific designs for compliance.

SOURCE: The President's Council on Competitiveness, Report on National *Biotechnology Policy*, 1991.

with **increasing numbers** of microbial pesticides, the Office of Toxic Substances has had few recent applications for planned introductions of recombinant DNA modified microorganisms and the subject matter of its applications has been limited narrowly to nitrogen fixation. The time required for, and general types of steps involved in application and notification processes are roughly comparable for the two agencies. From 3 to 6 months seem to be required for these processes. APHIS, with its large body of experience, probably has the most regularized review processes today.

Coordination With States

A few State governments independently have promulgated deliberate release regulations (see State and Local Government). Most feel that effective coordination with the Federal agencies will suffice.

The COC's Biotechnology Working Group is charged with coordinating Federal laws, regulations, and poilcies with those at the State level. As a practical matter. the task of coordination lies with the individual agencies themselves. USDA and EPA use State input in different ways. Based on its traditional network of connections with State-level agricultural departments, USDA has explicitly incorporated State review applications for field tests into its overall review process. USDA also has brought together Federal and State regulators of biotechnology in annual national meetings. EPA, on the other hand. does not have a tradition of elaborate, direct connections to State environmental departments. Recently. EPA has attempted to identity biotechnology "point people" in State environmental departments (68). However. many State regulators may not feel "bin the loop" in terms of knowing what EPA is doing in biotechnology regulations and how their State should play a part (64, 93). EPA pubilcty acknowledges the importance of receiving State input. **but procedures** for gathering this input are far less for**malized than is the case in USDA.** Still, EPA's TSCA Office did consult with State regulators for each of Biotechnica's seven field test requests (32). For the relatively few release PMNs handled, EPA-OTS has developed an informal set of steps to:

- **include telephone contact with the appropriate State regulatory** agency or agencies concerned with a particular submission;
- make available a nonconfidential version of the PMN on request;
- include State personnel in a site visit;
- make available public docket materials on request;
- provide opportunity for State personnel to comment on the Agency's draft risk assessment; and
- give State personnel a draft of the TSCA section 5(e) order. with conditions for the field test (30).

Coverage

Scope

Possible Gaps—Some concern has been voiced that under the current allocation of regulatory responsibility for biotechnology, some releases might slip through the cracks. An often cited potential gap in jurisdictional authority pertains to genetically engineered plants that are neither pesticidal nor themselves plant pests. In such a case, where neither EPA-FIFRA nor USDA-APHIS has clear responsibility, the question has been raised, who would have oversight over field trials'! (35)

In the past, regulatory oversight for field trials largely has been allocated with "traditional" recombinant DNA in mind. Even newer techniques have arisen. however. such as biolistic or gene gun approach to injecting genes into organisms. How will the new techniques being de-

veloped fit into the oversight structure'? Should they be? Can the experience base derived from "traditional' recombiant DNA be applied to new techniques?

As the science of biotechnology advances. it is likely that genes of more than one trait will be inserted into a plant variety being developed. This mixing of genes could lead to an overlap of authority. For example. a *Bacillus thuringiensis gene* for pest resistance could trigger EPA review under FIFRA in a food crop; a gene for a nutritional component could trigger FDA responsibility: while the use of a plant pest vector could trigger USDA oversight. Even though USDA-APHIS and EPA-FIFRA have a history of cooperation, some difficulties could arise in treating such situations. A company might have to submit three packages for review due to the different roles of each agency. This could comprise a regulatory burden.

It also has been asserted that. apart from federally funded research, Federal oversight of genetically engineered animals is limited to selected invertebrates and animals with genetic material from plant pests. While most livestock animals would probably generate little risk to the environment if genetically engineered, aquacultural species have been cited as potentially more problematic. The possibility of escape of genetically engineered fish from outdoor aquacultural ponds to watersheds. where interbreeding with natural populations could occur. gives rise to ecological concerns *(35). (See* box 7-D.)

Thus, while some observers are concerned about possible limits to and gaps in Federal oversight of transgenie plants and animails. some assert that by far most cases of release of transgenic *animals wuld* **be covered** by USDA Science and Education (for research), USDA-APHIS (for plant pest invertebrates and animals carrying animal diseases). FSIS or FDA (for use of animals as food). FDA and APHIS (for animal drugs and biologics). and the Public Health Service (for interstate movement of etiologic agents that carry human disease.) Only research not receiving Federal funding, in which the animal is not a plant pest. not an agent for animal or human disease, not given a drug or biologic. and not to be sold as food (92) could constitute gaps in oversight of transgenic animals. Thus, while some observers are concerned about possible limits or gaps in Federal oversight of transgenic plants and animals, others expect the natural evolution of oversight to occur. It remains to be seen whether the regulatory framework is flexible enough to catch such cases, and how, for example, the system handles genetically engineered plants that are neither engineered for pest resistance nor themselves plant pests.

Current and Projected Treatment of Such Organisms and Products—For its part, USDA-APHIS seems to be willing to extend its range of oversight regarding genetically modified plants. Plants' abilities to act as pests can be viewed in a broad context. Potential disruption of the environment by novel plants could in the broadest sense qualify a plant as a potential pest. Some environmentalists feel that USDA already is stretching its statutory scope to deal with biotechnology, and may not have the authority to extend its scope still further.

Box 7-D—Fish Regulations: Something To Carp About?

The gene that regulates growth in the rainbow trout was transferred into carp by a team of scientists from the University of Maryland, Auburn University, and Johns Hopkins University. In experiments to date, the carp have grown 20 to 40 percent larger than their unmodified relatives. Among some participants in the fish farming and research industry, enthusiasm runs high over the prospect of impacting the Nation's $900 million fish farming industry and, eventually, helping to feed the hungry of the world. Others emphasize caution. The American Fisheries Society, composed of fisheries scientists, has recommended close monitoring by the Federal Government, tight control over the environmental release of a modified fish, and sterilization of the fish (75).

The transgenic fish project was started in 1986; in February 1990, USDA approved the project but protests from four public groups persuaded the North Auburn Fisheries Research Unit, at Auburn University, the site of the **project, to redesign the pond.** The new place was approved by USDA in November 1990, pending inspections early in 1991.

Current design places the fish in 10 outdoor earthen ponds, set on concrete stabilizers, surrounded by chain-link fences covered with bird netting, double and triple screened drains and ditches. Beyond these is a 17-acre lake filled with predatory fish, and then a pond with chemical and mechanical barriers before the local creek (1).

SOURCE: Office of Technology Assessment, 1992.

Exemptions—Exemptions, as opposed to accidental gaps in coverage, are cases or classes of planned introductions deliberately excluded from regulation. Many questions underscore the dynamic, evolving nature of the regulatory situation. For example, will—or should—the trend toward examining new products of biotechnology carry over to the products of ''traditional field trials. which now are exempted implicitly from review'? Or, as novel techniques become more familiar, will they be less likely to serve as triggers for product review? In other words, will we learn enough to exempt certain products resulting from certain biotechnology techniques'?

The NIH RAC has relaxed its recombinant DNA Guidelines as an increasing experience base has indicated the appropriateness and safety of so doing. The 1989 National Research Council's report on biotechnology endorsed such an experiential approach to environmental releases:

> As field tests are performed, information will continue to accumulate about the organisms. their phenotypic expression, and their interactions with the environment. Eventually, as our knowledge increases, entire classes of organisms may become familiar enough to require minimal oversight . . . (73).

The 1990 draft Scope principles reinforced the idea that information-based familiarity can lead, when appropriate, to exclusion from oversight. Both EPA and USDA endorse the concept that biotech oversight can evolve on the basis of information gathered. Already, these agencies are beginning to exempt from review or expedite review of certain classes of organisms or products if certain conditions are met (65).

EPA Definition of a Microorganism as a Chemical Compound

The application of TSCA to biotechnology has raised some controversial and as yet unresolved issues. Paramount among these concerns is the inclusion of biotechnology products under the definition of a chemical substance, whence EPA draws its authority to regulate genetically engineered microorganisms. Although it is clear that DNA molecules can fall under the definition of chemical substances, it is less clear whether the host organism can be so defined. On the one hand, Witt writes: "Calling microorganisms chemicals is tantamount to calling chemists chemicals—or regulators chemicals. On the other hand, some in industry feel strongly that microorganisms have uses that are directly connected to their chemical nature and that EPA jurisdiction is very reasonable (107). EPA's interpretation has on occasion been called "ripe for litigation" (53).

In any case, it is unclear "whether the scheme of regulation envisioned and currently employed for conventional chemicals is suitable for oversight of biotechnology' (48). Regulatory approaches for chemicals may be difficult to apply to living organisms. Indeed, the fact that TSCA regulations for biotechnology products have not yet been finalized, despite having gone through various iterations, may result in part from the difficulties inherent in manipulating rules conceptualized for chemicals into rules appropriate for living organisms, although EPA has reviewed microbial PMNs under TSCA since 1986. Other problems may include technical difficulties in defining ''new organisms, interagency disagreements, interpretation of 'commercial purposes, and the small-quantities exemption. Nonetheless, the intent of Congress that TSCA serve as gap-tilling legislation seems to invite its use for some biotechnology products that would otherwise have no obvious regulatory home. From the coordinated framework, the role of TSCA in biotechnology seems to have been accepted. on at least an operational level, even it' the broad definition of a chemical compound has not been universally popular.

The trigger under TSCA for PMN is manufacture of a chemical, not the issue of safety. Therefore, when this traditional trigger for TSCA is applied to biotechnology, it is not consistent with the emphasis based on technical risk in the Scope Principles. It is often argued, however, that since all new chemicals must be reviewed. no implications of risk are ascribed automatically to biotechnology products falling into this net.

Commercial v. Research Authority

EPA—Because TSCA is a commercial statute, it arguably does not apply to the deliberate release of genetically engineered microorganisms in nonindustrial settings. EPA currently requests industry to comply voluntarily with the PMN requirements for commercial R&D involving field test releases with intergeneric microorganisms. Academic researchers performing comparable releases may be seen as left out of the loop, in a regulatory limbo. Congress expressly exempted small-scale research and development from TSCA authority. Much depends on the breadth of EPA's interpretation of "commercial purposes. For example, academic research may be colored by commercial intent because it maybe funded by an industry source: because patent rights are assigned to a company for commercial development; or even because a researcher's home institution receives private-

sector funding. One possibility is that all field test releases will count as commercial in intent. However, problems may arise with a broad net approach. Other agencies, as well as universities, may question the validity of this approach. EPA's possible move into the R&D laboratory under a similar approach is likely to arouse fears of excessive layers of bureaucracy among laboratory researchers.

USDA—The possibility of EPA penetrating further and further into the realm of research, despite its commercial mandate, has a counterpoint: USDA appears to be exploring ways to step back a pace from its review of field trials conducted as academic research. The agency's "Proposed USDA Guidelines for Research Involving the Planned Introduction in the Environment of Organism With Deliberately Modified Hereditary Traits." (FR56 (22):4134–4151) seems to place much of the weight of the research review process at the institutional level, with the goal of minimizing the weight of bureaucracy on researchers while still ensuring safety. The agency's Agricultural Biotechnology Research Advisory Committee (ABRAC) played a substantial role in developing these guidelines. It is important to note that, in any event. these guidelines are just for USDA-funded research; APHIS still supplies the principal regulatory coverage.

Criticism of the current situation regarding research includes alleged confusion over agency jurisdictions. For example, when Biotechnica International field tested genetically engineered nitrogen-fixing bacteria. it did so under a 1989 consent order from EPA. However, when a researcher at Louisiana State University sought to do followup studies at the site, State officials, various Federal officials, and ABRAC became involved as EPA oversight and jurisdiction became less evident. EPA clarified its position with State officials, and USDA agreed that EPA would maintain jurisdiction until it chose to relinquish that jurisdiction. While the main question appears to have been over the research value of continuing to monitor the site. rather than any safety question. it demonstrates some degree of uncertainty over jurisdiction (26).

Potential Impacts of Regulation

Negative Impacts

Questions have been raised regarding the short-and long-term impacts of' the regulatory climate on research. It is frequently postulated that academic researchers do not possess the organizational whet-withal to proceed through a regulatory maze, and may find the bureaucratic and financial weight of regulatory approval procedures so burdensome that they will choose not to carry experiments through the field trial stages (74). This perception could block research at a key step, since the field trial is the stage at which * 'the rubber meets the road, at which the predictions of the lab are tested in the real world. The impacts on research of the rulemaking process in Federal regulation of biotechnology were explored in a national survey conducted in 1989 (52, 83). Of 355 responses to the question. ''Have you ever been discouraged from conducting field tests with genetically modified organisrns?," 16 percent said yes. Among private-sector responders, 23 percent felt they had been constrained. Some 12 percent of responders replied that they had chosen not to proceed with a field trial even though they had a genetically modified organism ready. Legalities, uncertainties about regulation, time needed, and paperwork required were cited as reasons for the decision not to proceed (52. 83). Criticism has been leveled as to the methodologies employed in the survey. Whether or not the percentages point to a dramatic ''regulatory burden on research seems open to interpret at ion.

Some feel that the survey captured a real reluctance among some researchers to go through the field trial. In any case, it is not clear that regulation rather than tough resource allocation decisions drives the decision to delay (or forego) field trials (83).

A 1990 survey based on personal interviews of 35 researchers and regulatory affairs specialists revealed overwhelming agreement that the coordinated framework is working and that APHIS is helpful and timely in its response to permit requests, while EPA seems to be improving. Most responders, however, asserted that biosafety and biological monitoring protocols were overly cautious, with potential implications for allocation of personnel time (16).

A third study surveyed 430 recombinant DNA scientists regarding their perceptions of the influence of activist pressures on recombinant DNA research. Some 63 percent view current safety mechanisms as adequate and 26 percent view them as overstringent; many perceive public controversy and litigation as having led to unwarranted obstacles in the regulatory arena (81).

A premise of USDA's Proposed ABRAC Guidelines is that the local Institutional BioSafety Committees (IBC's) can provide helpful advice to academics, streamlining the regulatory procedure. According to the level of safety

concern, IBC oversight ranges from simple notice to IBC review and either approval or disapproval by the IBC and the USDA. Since IBC's previously have dealt principally with laboratory-contained experiments, they may require training to play a helpful role at the field trial stage; more agriculturally and ecologically trained members will need to be added. The University of California system-wide biotechnology program has sponsored an educational meeting for institutional biosafety officers who can work with the IBC's on matters of deliberate release (43).

Possible Positive Impact on Research

Although regulations of genetically engineered organisms may possibly inhibit one line of research (field trials). it may stimulate another—ecological research. As risk assessment methodologies are being devised for evaluating releases of recombinant DNA modified organisms into the environment, ecologists and population biologists are turning their attention toward related questions. The Ecological Society of America report on deliberate release describes a pressing need for interdisciplinary research (99). The concept of deliberate release has provided a compelling focus for questions of ecological community dynamics, migration of genes into populations, evolutionary change, and other fundamental problems. Furthermore, many researchers are stimulated by the opportunity to channel their research toward a useful analysis. Such lines of work do not fall neatly into most categories of research funding; thus funding sources may need to adjust their emphases since this work has an important role to play in the evolution of agricultural biotechnology. The 1990 Farm Bill addressed this need by setting aside funds for risk assessment research, equaling 1 percent of whatever the department spends in biotechnology research. Questions pertinent to risk assessment research, as well as the relationship between ecological research and risk assessment are described at greater length in chapter 8.

As guidelines are finalized and disseminated, and risk-assessment research proceeds, regulatory uncertainty should be reduced for researchers. With reduced ambiguity, as well as steady increases in information and experience, researchers may well venture more boldly in greater numbers into the field trial stage. Institutional BioSafety Committees may become better versed at giving advice and assistance to researchers, as may other university offices and field trial supervisory staff. Thus, the potential negative impacts on research **could** prove to be short-lived. In the future, technology transfer of genetic engineering advances may be mediated through industry-sponsored, university-based field trials. Although many companies would prefer to keep work 'bin-house. ' others may place greater value on the objectivity y of university research and the capacity of university facilities. While possible contlicts of interest would have to be resolved, both parties could thus continue to contribute to field trial research. (See box 7-E.)

The positive stimulus of the regulatory climate to ecological research may be at or nearing its peak at this time: in the short- and mid-term, assessment methodology will be developed and refined. Data gathered will be synthesized. Eventually, in the long run, assessments of the results of releases may well become yet one more subfield of ecological research, one more way to approach interesting problems that exist in a real-world context.

Impacts of Regulation on Agribusiness

Only half of the agricultural biotechnology companies surveyed by Burrill and Lee (7) consider Federal agency jurisdiction over the testing and selling or distribution of biotechnology products clear-cut. Nonetheless. only a minority believed that they had experienced Federal regulatory delays. Some 16 percent found delays in relation to product testing; some 16 percent found delays in relation to selling and distribution (7).

For the most part, at least the large agricultural companies find that the APHIS system is predictable and works well, without inhibiting industrial activity (38, 40). Moreover, even those concerned with the competitiveness of industry also acknowledge the role of regulations in ''shielding" industry from unfortunate occurrences that could. by thus capturing public attention. slow commercial product development (79).

At least one small start-up agricultural biotechnology company, Calgene. has fared well under the current regulatory structure; between November of 1987 and October of 1990, Calgene received approvals from USDA for some dozen field trials for three genetically engineered crops in five States; the average approval time of 113 days is viewed as extremely reasonable. Representatives of Biotechnica, Pioneer, and Northrup King have also testified as to the effective workings of the APHIS system for genetically engineered plants (89).

It has long been alleged that the strategic business plans of some smaller companies may have been, and may continue to be, influenced by the regulatory climate, as well as by public concern over biotechnology. The company Mycogen, for instance, deliberately used killed rather than living recombinant bacteria as pesticides; Ecogen

Box 7-E—EPA Research and USDA Research

EPA has established a research program focused on the use of microorganisms in biotechnology and intended to meet the technical needs of the regulatory program. The six areas of research are as follows:

1. development of methods for detecting, enumerating, and analyzing microorganisms in complex samples from a variety of real-world habitats;
2. development of data and predictive models related to transport or spread between the point at which release occurs and other locations;
3. determination of potential for survival, growth, or colonization of released microorganisms under various conditions and environments;
4. assessment of factors affecting stability of genetic material and likelihood of gene exchange;
5. detection of any negative environmental response; and
6. criteria and methodologies for controlling risk.

Inhouse EPA scientific staff are developing a complementary extramural research program. Regular independent peer review is intended to keep the orientation of the research toward the risk assessment needs of the regulatory staff while still encouraging scientific quality and contributing basic information on microorganisms in the environment (67). The Research Office is thought to have worked very closely with the FIFRA staff, directing research towards assistance in developing evaluation procedures. The biotechnology assessment budget, however, was cut in 1991.

The 1990 Farm Bill (S. 2830) contained provisions governing USDA research. In addition to promoting Federal funding for "high-priority research" in areas including biotechnology, the bill created a Biotechnology Risk Assessment Research Program. A competitive research grant program is authorized for environmental assessment research "to the extent necessary to help address general concerns about the environmental effects of biotechnology"; research is authorized that will assist regulators as they develop policies on planned release. Eligible areas of research include: biological and physical containment methods, methods of monitoring dispersal of genetically engineered organisms, and gene transfer between genetically engineered organisms and related cultivated or wild species. The Secretary of Agriculture is required to consult with APHIS, ABRAC and OAB on specific areas of research (44).

SOURCE: Office of Technology Assessment, 1992.

has developed products with naturally occurring or nonrecombinant organisms (33). DNA Plant Technology (DNAP). which has to consider agricultural and food regulations, has deliberately adopted a "bifocal' business development approach, developing products through innovative uses of nonrecombinant technologies, such as tissue culture, as well as exploring the potential of recombinant plants. This reduces their vulnerability should regulations for the commercialization of biotechnology prove untenable to them. While DNAP currently has one regulatory staff member, it foresees the likelihood of adding more (20). With training in use of the "Intelligent Form Generator, " a software program designed by the National Biotechnology Impact Assessment Program to walk scientists through the production of an application, the NBIAP program director predicts th\aut a field trial application can be generated in less than 2 hours. Without this computer aid, he estimates. completing an application could take 1 to 2 months, with a staff, and up to 6 months without a staff (3). Resolution of regulatory processes and ambiguities will be critical as companies ready themselves to move to large-scale use of recombinant plants.

One point raised by the private sector is the need for clarification of EPA role under FIFRA regarding transgenic plants with pest-resistant properties. Clarification of scope of review, preparation of a guidance document on data requirements, and harmonization with APHIS are regarded as necessary to reduce regulatory uncertainty for industry (37, 109).

The vast magnitude of trials necessary for the development of any new crop variety makes it particularly important to clarify regulatory roles and requirements with respect to recombinant technology. The seed company ICI Garst, for example. has compiled figures on the development of corn varieties (82). In 1990, some 350,000 plots were used for nonrecombinant plants. The following numbers demonstrate the sheer number of lincs involved in generating new varieties in 1990 and expected in 1994 (table 7--l).

Table 7-4—Genetic Lines Needed for New Corn Varieties

Stage of developement	Number of Lines 1990	1994
New inbreds	79,000	92,000
Preliminary hybrids	34,000	39,000
Advanced hybrids	5,600	8,000
Experimental hybrids	1,600	2,400
E - hybrids	125	150
R - hybrids	30	30
N - hybrids	10	12
New commercials	9	9

NOTE: E-Hybrids are hybrids exchanged among breeders with the company; R-Hybrids are regional uniform strip tests; N-Hybrids are national uniform strip tests.

SOURCE: ICI Garst Seed Co., 1991,

Obviously, were genetically engineered plants involved in such trials, and if these had to pass a complex set of regulatory requirements, agricultural companies would be forced to weigh their options very carefully. The costs of meeting regulatory requirements might prohibit them from bringing promising recombinant plants to full commercialization as new varieties. On top of the sheer numbers involved, another key point is that multitrait selection is the normal approach to plant breeding and development of improved varieties; the approach is to improve a number of traits concurrently; multiple recombinants might be combined in different trials. **Furthermore,** seed from the later stages of testing is sold. Agricultural practices do not separate variety from variety; all seed corn is stored in grain elevators in bulk. Clearly this is not a set-up readily amenable to special treatment for biotechnology. The restrictions governing small-scale field trials would be logistically infeasible. Developing even a conventional hybrid can cost approximately one million dollars. Although biotechnology can improve efficiency in the early research stage, by making new genes available quickly and precisely, industry emphasizes that the rigors—and the orders of magnitude-of the hybrid testing scheme will not change.

Thus, the regulatory climate will have a significant impact on whether or not biotechnology is widely used as a tool in the seed industry. Assessments of the impact of regulations on industry will need to take this into account. A responsible but reasonable and clear regulatory path towards commercialization will be crucial to the successful implementation of biotechnology in agriculture.

Public Participation

The U.S. public today questions the use of new technologies . Based in part on general environmental awareness, skepticism about science, and negative experiences with the chemical industry and the nuclear power industry, this questioning attitude is now a potent force. Today, many analysts of biotechnology sound the clarion call of public participation; if the public is to accept biotechnology, people must have access to information, and be able to play a role in debating controversies, and achieve a sense of trust in policy makers (54, 90). Federal regulatory agencies sometimes do not receive the full trust of the public. State agencies tend to be somewhat better trusted. When Federal agencies share information and involve the public, they are likely to build confidence in their procedures. FDA attempted this by publishing scientific information relevant to its decision on bST in *Science.* The meetings for media and other segments of the public held by USDA represent another example of public confidence-building through involvement. A positive public perception of biotechnology is obviously critical to its growth; beyond this, participation by the public **can contribute to the beneficial development of biotechnology; questions** raised can indeed be pertinent. Although the public has channels through which it can participate in regulations. it may not be aware of them.

For example, public input into the review process for field trials is officially ensured through notifications in the Federal Register. Environmental assessments and pending approvals are so published. Clearly, however, the ‘‘general public’ does not as a rule pore through the Federal Register. Various environmentalist and public interest groups do, however, and can bring matters to a wider audience. In some cases, such groups challenge approvals. For example. ice field tests (102) of ice-minus bacteria used to protect crop leaves from frost in 1987 were significantly delayed due to such challenges. A very narrow nongovernment subset of the public is brought into the picture when scientists external to the agencies perform scientific reviews to augment staff review in problematic cases.

Public input also can arise when States receive field trial applications from the Federal agencies. Depending on an individual state's review process, representatives of the public may well participate. The 1990 Special Workshop for State Agencies, “State Oversight of Biotechnology, came to consensus on the importance of a public participation component for any State biotechnology task force (39).

At the institutional level, public membership is mandated for Institutional Biosafety Committees (IBC’s), which seem likely to be called on more and more frequently to

examine plans for field trials at an early stage within institutions.

One somewhat sensitive area in terms of public participation is that of confidential business information. As discussed earlier. Federal agencies have the legal right to protect confidential information deemed critical to a company's competitiveness. In fact, companies submitting applications for field trials can submit two forms of an application. one for in-house review. under confidentiality terms. and one with confidential information deleted. for open distribution. Only the few States with legal protection for confidential business information can be sent the complete form. Of course, the more blanks that appear in an application, the more likely that proposal will be regarded with public distrust or unease. To minimize public unease, Federal officials encourage companies to keep their designated CBI to a minimum. Complaints have been voiced when information unnecessarily designated as CBI has been unavailable to the public (35).

Public input into the process leading toward field trials has changed since the early and mid 80s, when court injunctions and vandalism were commonplace. Relative acceptance of the role of field trials and their safety has grown. Indeed, evidence exists that, together with an increased experience base, positive public involvement in biotechnology regulation can expedite the field trial process. (See box 7-F.)

The quieting of local public opposition to biotechnology field trials seems to be evidenced quite widely. The great majority of field trials approved at the Federal and State level have met with little if any opposition by the public (106).

Opposition activity now seems to be directed primarily at special cases. A current example is that of crop plants genetically engineered to withstand particular herbicides, which can then be sprayed readily over the field, as they will cause a problem only for the noncrop plants. Environmentalist spokespeople specializing in biotechnology are far from happy about this as a goal for agricultural biotechnology. In brief, despite industry protestations that this approach allows the strategic use of particularly benign herbicides, environmemtalists see this as a mechanism to excuse, if not encourage, application of environmentally hazardous chermicals. (See Goldburg et al., 1990 (36) for a thorough discussion of antiherbicide tolerance views; also Goldburg, 1989 (35).) Early in 1991, the National Wildlife Federation (NWF) petitioned the USDA regarding Calgene Inc.'s application to field test genetically engineered cotton in 12 States. Calgene's October 1990 application to USDA proposed a 25-site test of cotton engineered to break down the herbicide bromoxynil. Whereas Calgene maintains that use of this cotton would significantly decrease herbicide use. NWF has petitioned the USDA to halt this broadscale testing until a thorough risk assessment has been conducted as to the impact on aquatic ecology and human health (22). In this case, the value question relating to herbicide tolerance begins to be tied to questions of progressively larger scale release. moving toward commercial release.

The responses of public interest groups to large-scale releases may well intensify: it remains to be seen whether other components of the public will take a similar view. such that the current atmosphere of acceptance turns to opposition as commercilazation is approached. Significant factors will include: technical experience base derived f-rem small-scale tests to date, activism on the part of environmentalist groups, media attention. public confidence in the regulatory agencies. and public perception of-—-and education about—biotechnology and risk-benefit assessments.

If decisionmaking is to be informed. education of the public about biotechnology risks and benefits must take place. Many advise that the evolution of biotechnology regulations benefit from the hard lessons of other industries. such as the nuclear industry, and emphasize education of and participation by the public. Thomas Jefferson has been quoted appropriately in this regard: " If we think the people not enlightence enough to exercise their control with a wholesome discretion, the remedy is not to take it from them. but to inform their discretion'" (46).

Public perception of biotechnology has been analyzed by OTA (101), and others (50). Apprehension over the novelty and power of biotechnology is mixed with a desire for the products of biotechnology. Two biotechnology trade associations (the Industrial Biotechnology Association (IBA) and the Association of Biotechnology Companies (ABC) have prepared materials and established committees related to public education. USDA ran several meetings as early as 1987 to work with the media and others toward public eductaion. Many of the Nations State and university biotechnology centers view education about biotechnology as one of their principal roles. Increasingly, high school teachers are taking courses in, and teaching. biotechnology': the media also is becoming more

Box 7-F—Two Experiences With Public Response

In the early years of field trials, 1983-87, two sets of experiments involving ice-nucleating bacteria in California drew local public opposition as well as public interest group opposition. Suits were filed in the case of Tulelake, California, and an injunction was enforced against the University of California researchers until an environmental amendment was made; in the case of Monterey County, the County Supervisors, making use of their zoning authority, banned such experiments for 1 year, forcing Advanced Genetic Sciences (AGS) to go to the Contra Costa County's Board of Supervisors for approval. Although a legal challenge was not upheld, many of the plants were uprooted as vandalism. (AGS had aroused particularly negative response beginning in 1985, when it had tested the bacteria in trees on its headquarters' rooftop, without authorization.) Through the various vicissitudes, the University of California test was delayed from 1983 to 1987; the Advanced Genetic Science's test was delayed from late 1985 to spring of 1987 (102).

in 1988, Biotechnica International received Federal and State approval for a small-scale field test in Wisconsin of *Rhizobium* genetically engineered to increase alfalfa yield for which the PMN's had been filed the year before.

In 1987, Biotechnica had conducted an extensive community relationship program in the county and the state where the field trial was to take place. This program involved: presubmission briefings to opinion leaders; press releases and brochures in layman's language, including a risk-benefit, "Question and Answer" style brochure; public meetings in the county sponsored by the company as well "as attendance by company representatives at State government and legislature committee meetings; and media relations. For the first 6 months, interest was high in the community and a small group of activists opposed the trial. After the last public meeting in the summer of 1987, no further opposition emerged and, despite intense media interest, no demonstrations or protests occurred at the time of the test itself in April of 1988. For subsequent tests, the company has followed a scaled-down program of community relations, with substantially less community interest. The local comfort level with this biotechnology venture seems to have increased significantly (31).

SOURCE: Office of Technology Assessment, 1992.

sophisticated and therefore more able to convey accurately technical and issues in biotechnology.

Problematic Issues

USDA Conflict of Interest?

The criticism has been leveled that USDA faces an internal conflict of interest because it has a dual responsibility to promote research and to regulate in areas of biotechnology (49). USDA officials make the argument that the Department of Health and Human Services is in the same situation, but has the luxury of having its division of' labor more readily perceived by the public as distinct. Within the same Department of HHS. the National Institutes of Health have responsibility for research and the Food and Drug Administration has responsibility for regulation. A comparable, but less visible or publicly understood, division exists within USDA. The Assistant Secretary for Science and Education is responsible for biotechnology research activities (including those of the Agricultural Research Service and the Cooperative State Research Service), whereas the Assistant Secretary for Marketing and Inspection Services is responsible for departmental regulation of biotechnology [delegation of acthority by the Secretary of Agriculture, published July 19, 1985 (Fed. Reg. 29367 (1985).] APHIS and the Food Safety and Inspection Service (FSIS) are the USDA regulatory agencies involved (55). Coordination between the research and regulatory arms of USDA is the responsibility of the Committee on Biotechnology in Agriculture (CBA). The Office of Agricultural Biotechnology (OAB) is set up to develop policies and procedures for research in agricultural biotechnology, coordinate environmental safety review of proposed USDA-supported research with genetically y engineered organisms, provide staff support for the CBA, and provide staff support for the Agricultural Biotechnology Research Advisory Committee (ABRAC). ABRAC in turn is to review research guidelines and proposals and provide scientific advice to research and regulatory agencies in biotechnology (56).

The existence of these committees demonstrates that the research and regulatory arms of USDA do interact. In fact, the agency would be criticized if there were no attempts at coordination, although the degree of coordination actually achieved has been questioned. The co-

existence within one agency of NIH and FDA seem to set a relevant precedent. Conflict of interest may be avoideed within USDA by:outside Crotiques, such as advice from ABRAC and othcr external sources of review. as well as by the perception of. and loyalty to, distinct yet complementray missions on the part of APHIS and Science and Education.

Burden of Proof of Safety

U.S. society today desires a zero-risk society. Arising naturally from this attitude is a desire for regulatory agencies, or science, to prove safety. The agencies are attempting to build databases through small-scale field trials and, by analyzing and extrapolating from such information. to significantly reduce the probability of any risk occurring from larger scale releases. However, absolute proof of safety will never be achieved in biotechnology field releases, just as it will never be achieved in any other dimension of society.

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Chapter 8

Scientific Issues: Risk Assessment and Risk Management

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Scientific Issues: Risk Assessment and Risk Management

INTRODUCTION

The large-scale commercial use of agricultural biotechnology gives rise to several questions. Does the release of large numbers of genetically engineered organisms into the environment pose special risks'? If so, what is the order of magnitude of these risks compared to the risks of traditional agricultural practices'? What benefits offset such risks?

Generally, concerns about genetic engineering focus on:

- possible ''escape" of a genetically engineered organism, such that it invades new ecological niches or outcompetes naturally occurring organisms and becomes a pest;
- possible disruption of a delicately balanced ecosystem;
- possible direct risks to humans or wildlife;
- possible problems of gene stability and of gene transfer to unintended recipient organisms;
- possible impact on evolution; and
- the sheer "newness" of the technique.

This chapter addresses these concerns and describes the range of scientific views on biotechnology and risk. A consensus has developed that risk assessment is desirable and feasible. Risk assessment in general is founded on principles and methodologies that can apply to biotechnology. We know what questions to ask in assessing ecological risks of planned introductions. A knowledge base already exists pertinent to these questions and risk assessment studies on this topic are proliferating. Science-based risk management builds on this technical knowledge and on our capabilities for risk assessment.

Risk assessment methodologies and our technical knowledge base make it possible to conduct effective risk assessments of specific introductions and to manage risks of acceptable introductions. Science-based regulations are central to effective management of risk. A variety of scientific and agricultural methods can be used to manage risk in particular situations.

RISK ASSESSMENT

Concerns and Postulated Environmental Risks of Biotechnology

General Concerns

Questions arise concerning the impact of introduced genetically engineered organisms: What is the likelihood that such organisms will persist in the environment"? What is the likelihood that they will spread, constituting an invasion into the ecological community'? Will they become pests, with a deleterious effect on other species'? Will the expression of the gene itself lead to an unwanted effect on the ecosystem'?

Other questions have to do with the recombinant gene itself (38): What avenues exist for gene transfer within and between various species in nature'? How probable are such exchanges and at what rates would they occur. if at all? If introduced genes are transferred to genomes existing in nature. how well— and how stably—will the functions for which they code be expressed?

Finally, broader, more fundamental questions can be posed: Are we in fact dealing with a phenomenon so novel that we have no way of predicting outcomes, of Performing adequate risk assessment? Do we have a moral right to manipulate still further the species and the ecology of our planet'? Are we losing an intangible, aesthetic quality to our lives by so doing'? Can we at-ford to say no to the benefits that this technology can confer on agriculture

Concerns About Plants

Specific concerns relating to genetically engineered plants include the possibility that transgenic plants will persist and become serious agricultural weeds; that the transgenic plants will invade natural habitats and disrupt local ecological interactions; and that the pollen of transgenic plants will act as a vector. bringing the introduced genes to other species that may then themselves become problem weeds. The likelihood of such possibilities occurring remains somewhat controversial, underscoring the importance of information from field trials and research. It is noteworthy, however, that transfer of genes from conventionally bred crop plants to noncrop plants has not created obvious problems in the past, and that traditional crop plants rarely have invaded natural ecosystems (I 4).

lnvasions of plants (by seeds. fruits. or vegetatively reproducing units) involves dispersal, persistence. and establishment: all three stages must be ''successful if' engineered plants are to become weeds. For transgenes (introduced genes) to move from crop plants and cause or contribute to a weed problem, hybridization with a reproductively compatible species must occur. For tiny

given crop species, only a small number of the wild relative species that are reproductively compatible are actually likely to present serious weed problems; however, it is theoretically possible for a plant to become a weed in a novel environment *(43).*

One specific concern posed frequently by some environmentalists, among others (32), is that genes for herbicide tolerance might be transferred from crop plants to weeds. If this were to occur, natural selection could favor the trait in weedy neighbors of crops treated with the herbicide. With any use of herbicides, furthermore, increased selection pressure is put on wild species for any herbicide tolerance traits they might already possess. Such developments might lead eventually to increased use of chemical herbicides. A fundamental debate has arisen between industry scientists who maintain that crops can be genetically engineered to be tolerant of particularly ''environmentally friendly' herbicides and some environmentalists who say. essentially, that no new technology should be used to favor continued use of chemicals in the environment.

Concerns About Microorganisms

In part because they are invisible and relatively "unknowable, " microorganisms tend to elicit more concerns on the part of the public than do plants. Parameters of concern related to genetically engineered microorganisms include the possibility of gene transfer and recombination. the possibility of movement into new environments, and the possibility of infection of nontarget organisms. Questions asked include: Will genetically engineered microorganisms give rise to biological risks for humans or other species? Will they give rise to environmental problems'? Do we have the technical understanding to evaluate and predict any such problems'?

Whether bacteria, fungi. viruses, or baculoviruscs, microorganisms suffer from a bad reputation at the broadest level of public perception: they are. after all often equated with"germs. " One specific concern raised with regard to genetically engineered organisms is the possibility of genetic material from such organisms being transferred to human gut bacteria. The risk of infection of humans. or other deleterious effects, is clearly going to be examined for planned introductions of microorganisms. For example. among the questions raised by Monterey County staff considering the Advanced Genetic Sciences (AGS) proposal to field test Frostban[R] was whether or not the *Pseudomonas fluorescens could* ' 'sensitize or aggravate existing health conditions among sensitive human populatitons living near the proposed test site' (66).

To assess risk of problematic infection of humans by genetically engineered organisms. information must be available on exposure level. This hinges on such factors as bioavailability or likelihood of absorption into cells or tissues, specificity, and level of interaction possible of the microorganisms or their chemical products with nontarget (human) tissues; and potential of the microorganisms for colonization or infectivity. The degree of pathogenicity must be considered as well. Some relevant factors include virulence. Possession of toxins, host range, and relative susceptibility. Generally. risk assessment will factor in predictability of the behavior of the recombinant DNA identified microorganisms based on their parent organisms, as well as knowledge of specific recombinant techniques used (40).

Scientists' concerns focus less on pathogenicity and more on the possible impacts of genctically engineered microorganisms on the environment. Suggested impacts include possible influences on: indigenous population size. diversity of species. the ecological community. natural cycles, and evolution of the introduced organisms (76). Microbial environments are complex. By one estimate some 10^9 microorganisms, representing a variety of taxonomic groups, inhabit one gram of soil. Uncetanties exist as to possible consequences of sudden introductions on balanced microbial ecosystems (46). Microbial diversity in the soil is high (88). This limits the niches available to introduced mirorganisms (86). While introduced microorganisms may thus compete poorly. they may persist in low-density populations. A key issue is whether or nor an unexpected later resurgent bloom or population expansion from a low-density population can be reasonably envisioned (84).

Since microorganisms can and do change location. questions of dispersal—and possible subsequent reproduction in nontargeted ecological sites—also are raised. The ability of a particular strain to transfer genes to other specics will affect the likelihood of other microorganisms being affected in new. nontarget areas. All questions bearing on survival, multiplicaton, and dispersal of genetically enginered microoganisms: on possible exchange of genes between introduced and indigenous microorganisms: and ultimately on issues of environmental and public safety, are engaging attention of academic and industrial scientists, the public, and governmental regulators alike (22).

Views Held in the Scientific Community

Particularly in the early days. the issue of planned introductions of genetically engineered organisms sparked

a range of views on safety even among scientists (50). In the mid-eighties, microbiologist Winston Brill argued that. for centuries, traditional breeding has altered animals and plants without negative consequence: and that microorganisms, including pathogenic species, have been added to the soil in hopes 0ft beneficial impacts. also without negative consequences (7). His conclusion that these observations alone formcd a basis for risk assessments of' organsms that have had one or a few genes added drew fire from a group of ecologists (lo). These critics pointed out that mutations that increase an organisms niche range can be ecologically significant. and that some ramifications of an organism's impact on the environment are not predictable from knowledge of its introduced genes alone. Casc-by-case quantitative risk assessment for deliberate release was recommended.

In 1987, *Science* published side-by-side articles by Frances Shw-pies (75) and Bernard Davis (15). Sharples. an ecologist. reaffirmed the need for casc-by-case assessments, given the complexity of any organism's interactions with the environment. Molecular biologist Davis suggested that the experience of ecologists with introductions of higher organisms is less pertinent to risk assessment of engineered microorganisms than are the insights of fields mom concerned with the specific properties of those microorganisms: population genetics. bacterial physiology. epidemiology. and the study of pathogenesis.

The range of possible views on safty runs from "zero risk' to catastrophic risk'; those who presume " small-risk, pending research occupy the middle of the spectrum. In the mid-eighties, molecular biologists tended to stress the relavance of the safty record of laboratory biotechnology and graviated toward the ''zero-risk" end of the spectrum. Ecologists, who tended to stress the complexities of the natural environment. were less sanguine about potential risks. but stopped short of the cat astrohic-risk position taken by certain envronmentalists. An important distinction exists between ecologists and evironmentaists. The former are:

- scientists concerned with the fundamental properties, proccssscs, and components of ecological systems .

The latter,

- by definition, are concerned with various sociopolitical aspects of environmental quality and management. They may or may not be experts in understanding ecological processes and the organization of ecological systems (63).

Some environmentalists, keenly aware of problems posed by past technologies, argue that the proposed user of new technologies bears the burden of proving safety. Biotechnology proponents, in contrast, argue that any risks are to date hypothetical. so that the burden of proof should rest with the doomsayer (5 I).

In the late 1980s and early 1990s. discussion has increasingly centered around developing appropriate risk-assessment parameters and frameworks and designing regulator-y treatment according to risk. The current ''operational' approach is in agreement with analyses in key reports that will be described in the next section (50). ''Presumed small risk. or risk in exceptional cases. with research or risk assessment required. is becoming more of a common theme. Arguments are tending to become more refined. revolving about such issues as legitimacy of risk-assessment parameters; the degree to which lessor-is from past field trials can be generalized: correct assessment procedures for casc-by-evaluations; development of predictive science related to these issues; science-btised regulations; and scientific mainagement of risk. Today the imminence of large-scale release is bringing all these discussions into sharp focus.

Major Risk Assessment Reports

Introduction to Risk Assessment

Why Risk Assessment Is Needed-Society *today* has been ''sensitized' to technology the public, in all its many forms, looks at past technnologies—those of the chemical or nuclear industries for example-and sees negative outcomes that were not thoroughly considered prior to implementation of the technologies. Along with skepticism is a strong strain of environmentalism. a growing uneasiness that far too often, for our convenience. we carelessly and permantly harm the environment. Furthermore, however unrealistic it may be, a desire for ''zero-risk seems to underliie many responses to technology and to life in general today.

For these reasons as well as to achieve the fundamental objective of promoting safety it behooves regulatrs and other responsible parties to conduct reasonable risk assessments of new technologics. Biotechnology, in particular planned introductions of recombinant DNA-modified orgainisms. is among the technologies for which risk assessment is now done. This is necessary for regulators. important to the public's sense of cconfidence, and useful to ''users' of biotechnology'. including researchers in academdia, industry. and government.

Principles of Risk Assessment—' *'Risk"* can be defined as the potential for negative or adverse consequent to arise from an activity or an event (23). Risk also can be defined as the probability of an event occurring multiplied by the cost of its occurrence (44). Risk assessment can be viewed as ''the process of obtaining quantitative or qualitative measures of risk levels. including estimates of possible health effects and other consequences as well as the degree of uncertainty in those estimates' (23).

Risk assessment simply is an analytical tool that pulls together a great deal of diverse data in order to estimate a potential risk from an event or a process (81). Often, historical data on possible adverse consequences are difficult or impossible to obtain, making risk assessment ''an inexact process that attempts to characterize and quantify uncertainty, but never completely eliminates it. " Nonetheless, despite the limitations and challenges, use of risk assessment principles makes it possible to organize and interpret knowledge so as to improve the prediction of possible outcomes and ultimately to manage risk (23).

Risk assessment has been defined as a five-stage process:

1. *Risk identification—* defining the nature of the risk, source, mechanism of action, and possible adverse consequences;
2. *Risk-source* chracterization—characterizing the source of potential risk;
3. *Exposureassessment—* assesing the intensity. frequency and duration of human or environmental exposures to risk agents;
4. *Dose-response assessment—* assessing the relationship between dose of the risk agent and health or environmental consequences; and
5. *Risk estimation—* intergrating a risk-source characterization with an assessment of exposure and dose-response, leading to overt measures of the level of the health, safety or environmental risk involved (59, 92).

Clearly these stages can be adapted to fit a variety of kinds of risks, and the entire process can take several different forms. (See figure 8-1.)

The choice of an approach to risk assessment depends in large part on the extent and quality of available knowledge, degree of expected precision, and importance attached to outcomes at a low probability. Where the knowledge base is large and little uncertainty exists, a risk or hazard may be described quite readily and a more precise "deterministic consequence analysis" might even be performed. On the other hand, when less knowledge is available and the level of uncertainty is high. a qualitative risk screening may be all that is possible. perhaps leading to a more quantitative 'probabilistic risk assessment.

A much-used framework to assess risk is that developed for the evaluation of health effects associated with chemicals in the environment. This was endorsed by a National Academy of Science report (67) and refined at the Environmental Protection Agency (EPA). This chemical risk-assessment framework sometimes has been adapted for evaluation of planned introductions of recombinant DNA-modified organisms into the environment (13. 16. 30).

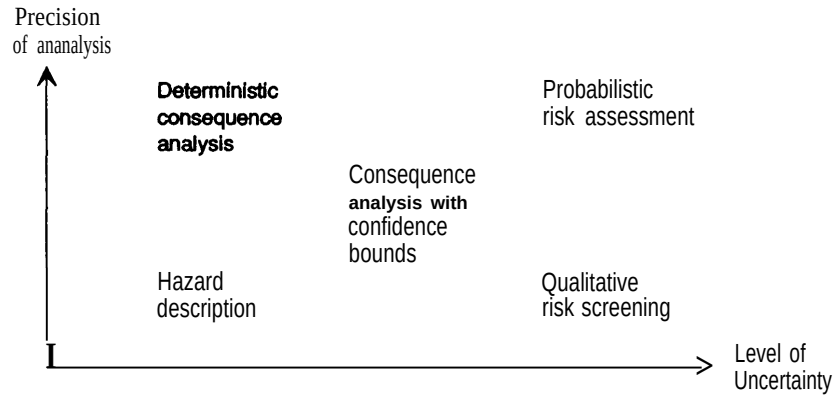
The National Research Council (NRC) and the Ecological Society of America (ESA) (69, 85) developed in 1989 risk assessment frameworks designed for recombinant DNA-modified organisms. But they were quite different from the chemical approach. The NRC procedure takes account of the degree of "familiarity"of a planned introduction; the ESA uses a risk attributes categorization; both lead towards the determintaion of an appropriate level of concern. While differing somewhat in perspective. the two approaches nonetheless resemble each other in basic conclusions and therefore together provide a solid framework for risk assessment of planned introductions. Clearly, choice of framework for risk assessment will influence the kinds of data required for evaluation and for permit applications (50). The two reports described below have had significant impact on the recent framing of discussions about planned introductions. Even proponents of chemical risk-assessment procedures point out that these procedures can be used to determine whether or not a particular organism should be evaluated intensively using an analogue of a chemical risk assessment (81).

National Research Council Report

Background—In late 1989, the National Research Council published *Field Testing Genetically Modified Organisms: Framework for Decisions.* This was requested by the Biotechnology Science Coordinating Committee (BSCC) on behalf of its member regulatory agencies. The report covered:

- plants and microorganisms,
- field-test introductions (but not large-scale commercial applications and related issues),
- environmental (but not human health) effects,

Figure 8-l—Alternative Risk Analysis Approaches



SOURCE: J. Fiksel and V.T. Covello, "The Suitability and Applicability of Risk AssessmentMethods for Environmental Applications of Biotechnology" in *Biotechnology Risk Assessment: Issues and Methods for Environmental Introductions (New* **York, NY: Pergamon Press, 1986), pp 1–34-**

- scientific issues principally (but not regulatory policy).
- field test conditions in the conterminous United States, and
- general procedures for determining categories (not specific case recommendations).

A fundamental principle underlying the study. and first introduced in an earlier National Academy of Science document (68), is that safety assessments of a recombinant organism "should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was modified. A related point is that ''no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular methods that modify DNA and transfer genes.

Topics analyzed for the 1989 report include: relevant biological characteristics of genetically modified plants; experience with genetic modification and introductions of plants modified ' 'traditionally" and by molecular genetic techniques; potential weediness: the features of the genetic modification in microorganisms; phenotypic characteristics of the parent organism and of its genetically modified derivatives: and relevant features of the environment into which the organism will be introduced.

Findings-The report recommends that the impacts of' genetic modification on the phenotype of the organism and the mobility of the altered gene be assessed. In some cases. when persistence of' the modified orgtanism is not wanted or when uncertainty exists as to effects on the immediate environment. risk assessment should emphasize the phenotypic properties relating to the persistence of the organism and its modification. Questions to be considered include: fitness of the genetically modified organism; its tolerance to physicochemical stresses; its competitiveness range of available substrates; and. if applicable. pathogenicity, virulencc. and host range. The report describes the long historry of safety in the useful employment of' plants and microorganisms. and underscores the need for field tests to increase the capability to assess any risks of large-scale introductions.

Specific scientific conclusionss of the report pertaining to plants include:

1. The current means for making evaluations of introductions of traditionally bred plants are appropriate (on the basis of experience with field tests of hundreds of millions of genotypes over decades).
2. Crops altered by molecular and cellular techniques should pose risks no different from those posed by crops modified by traditional genetic methods for similar traits.
3. The potential for enhanced weediness is the principal risk to the environment seen from introductions of genetically moditied plants. although the likelihood of this occurring is low.
4. Confinement by biological. chemical spatial, physical. environmental and temporal means is the principal means of maintaining the safety of field introductions of classically modified plants.
5. Experimental plants grown in field confinement rarely if ever escape to cause problems in the environment.
6. Established confinement options are equally applicable to field introductions of plants modified with

molecular or cellular methods and to plants modified with classical genetic methods.

Conclusions concerning microorganisms included:

1. Many molecular techniques make possible genetic changes in microbial strains that can be fully characterized.
2. The molecular techniques are powerful in their capability to isolate genes and transfer them across biological barriers.
3. Field experience has given rise to a great deal of information about some microorganisms; nonetheless, less information exists on microbial ecology and less experience with planned introductions of genetically modified microorganisms than there is for plants. No adverse effects have been noted from microbial introductions to date; a field test should go forward when sufficient information is available for its safety evaluation.
4. The probability of adverse effects can be minimized or eliminated by appropriate means of confining the microorganism to the environment into which it was introduced; one example would be the use of "suicide genes.

The framework for evaluating risk developed in the report is structured around the following questions:

1. **Are we** *familiar* **with the properties of the organism and the environment into which it may be introduced?**
2. **Can we** *confine or control* **the organism effectively?**
3. **What are the probable** *effects* **on the environment should the introduced organism or a genetic trait persist longer than intended or spread to nontarget environments? (69)**

The familiarity criterion is key to this report and has reappeared consistently in risk assessment discussions since. Familiarity means having sufficient information on which to base a reasonable assessment of safety or risk. Thus, as our information base increases, so does the scope of "familiarity." When the familiarity criterion is not met. the possibility of confining or controlling the organism and the potential consequences of failing to control it must be evaluated.

The report is intended to provide a basis for a "flexible, scientifically based. decisionrnaking process. The classification of an introduced organism into a particular risk category is made possible by the framework for evaluating field tests (69).

The 1989 NRC report is often cited and has provided a conceptual framework for many approaches to risk assessment of planned introductions of genetically engineered organisms into the environment. Its level of detail made it more palatable to technical audiences than the 1987 pamphlet, which was at times criticized for making assertions without documentation (11, 50).

The Ecological Society of America Report

Another seminal assessment was published in 1989, *The Planned Introduction of Genetically Engineered Organisms: Ecological Consideratons and Recommendations (85).* This report was prepared for the Public Affairs Committee of the Ecological Society of America (ESA) and also has been broadly disseminated and cited. Dr. James Tiedje chaired a workshop committee in April 1988, examining ecological aspects of planned environmental introductions of genetically engineered organisms. The Workshop Committee's initial draft was reviewed at great length by the ESA Public Affairs Committee, the ESA Executive Committee, and other ecologists. The report

> supports **the use of advanced** biotechnology **for the development of environmentally sound products. and states that the phenotype of a transgenic organism, not the process used to produce it, is the appropriate focus of regulatory oversight. Ecological risk assessment of proposed introductions must consider the characteristics of the engineered** trait, **the parent organism, and the environment that will receive the introduced organism (85).**

Like the NRC report, the ESA report emphasizes product, rather than process, as the appropriate focus of evaluation and regulation. Thus, ''genetically engineered organisms should be evaluated and regulated according to their biological properties (phenotypes), rather than according to the genetic techniques used to produce them" (85). Yet the report acknowledges the potential for novelty and consequent likelihood of evaluation inherent in the new techniques. The report acknowledges, however, that ''because many novel combinations of properties can be achieved only by molecular and cellular techniques, products of these techniques may often be subjected to greater scrutiny than the products of traditional techniques. Moreover, it recognizes that even precise genetic characterization of transgenic organisms does not necessarily allow scientists to predict all ecologically important expressions of phenotype in the environment.

The ESA report emphasizes the importance of considering a variety of ecological factors in ecological ramifications of planned introductions. Among these are

survival, reproduction, interactions with other organisms, and effects on ecosystem function and dynamics. Potential undesirable impacts must he weighed in evaluations. While explicitly calling attention to the complexities of ecological risk assessment, the report supports the position that "ecological oversight of planned introductions should be directed at promoting effectiveness while guarding against potential problems. Thus, the authors observe that most cases will present a minimal risk to the environment and provide a set of specific scientific criteria for ''sealing the level of oversight to individual cases. The four categories of criteria included:

1. attributes of genetic alteration,
2. attributes of the parent organism,
3. phenotypic attributes of the engineered organism in comparison with the parent organism. and
4. attributes of the environment.

Specific attributes are grouped according to level of risk presented and corresponding level of scientific risk assessment needed. Coming as it did from a group of ecologists, the ESA report is often cited as a touchstone for those wishing to balance the positive potential of biotechnology with a sensitivity to the environmental consequences of actions.

Biotechnology Ecological Risk Assessment

Introduction

A central goal of ecological risk assessment of planned introductions of recombinant DNA-modified organisms is to ''make a reasonably accurate prerelease prediction of the behavior an organism is likely to exhibit in its new ecological context and given its particular genetic modification, and to be able to detect and avert potential problems before they occur" (76).

Most scientists seem to concur that the focus of risk assessment should be on a particular organism, with its characteristics (genetically modified or not) and the genes that code for them, in a particular environment. Experimental protocols for ecological risk assessments need to be refined to screen out potentially problematic introductions before release (l4).

While scholars argue as to which risk assessment model would best apply to environmental introductions of recombinant DNA-modified organisms, all agree that the complexity of ecological factors renders biotechnology risk assessment particularly challenging. Living organisms can change locution, reproduce, and perhaps exchange genes. Once released into the environment. they will interact in a dynamic fashion with other species. They are indeed different from chemicals.

Ecological risk assessment is a still young methodology, and not standardized. Some argue that directly relevant data are scarce enough, and ecological phenomena are sufficiently complex that resasoned qualitative judgments are more feasible than more precise quantitative assessments. In practice, expert review panels using good scientific judgment and common sense. along with guidelines of points to consider, achieve qualitative assessments of the riskiness of various combinations of factors. As experience is gained. codification of the principles of review should evolve for application to future cases. Augmentation of" human judgment with knowledge system technology has been suggested as a means of facilitating the process (24, 66).

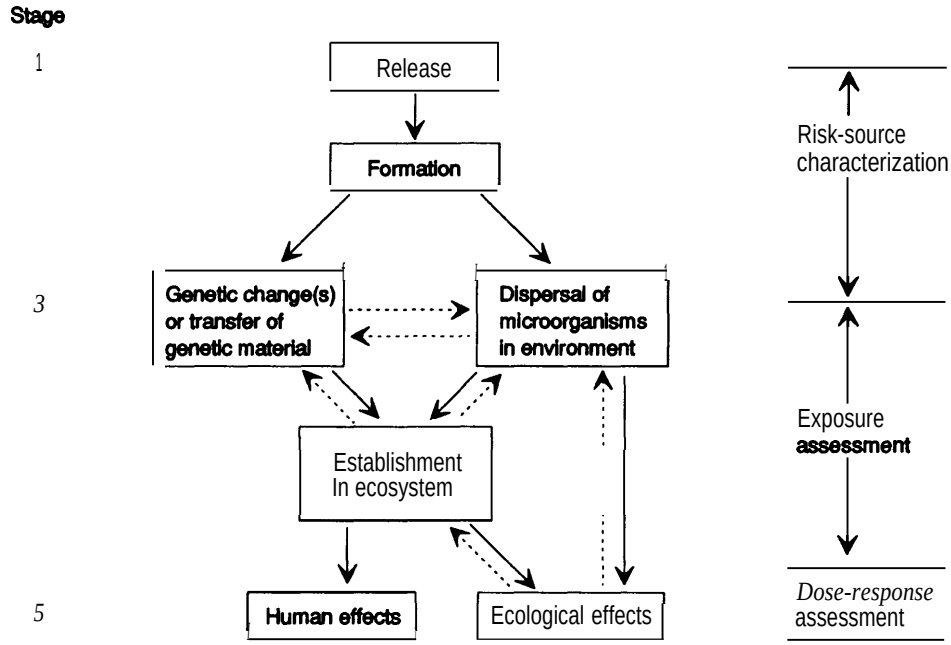
One way of conceptuall y applying risk assessment procedures to planned introduction of recombinant DNA-modified organisms into the environment is to match the three classic risk assessment stages (A. risk-source characterization: b. exposure assessment: and c. dose-response assessment) with the five stages involved in planned introductions. (See figure 8-2.) Information about stage one. *formation of a* recombinant DNA-modifiedd organism. and stage two, its deliberate release or accidental escape into the environment contributes to risk-source characterization. Exposure assessment would take into account data on stage three. *proliferation of* the organisms, including dispersal and possible exchange of genetic material, as well as stage tour. their *establishment* in an ecosystem. Stage five, human and ecological effects, relate quite directly to dose-response assessment (23).

Another way of looking at risk assessment of planned introductions is to consider the defination of "risk" as the product of' ''exposure' and "hazard." Exposure is related to the possibility of escape of the arganism, its survial. reproduction. and spretd. as well as to the gene transferred and the vector, if present. Assessment of the hazard, or potential environmental impact. depends on the ultimate fate of the introduced organism-whether it becomes extinct. establishes a balance with indigenous species. or overruns the recipient environment (53).

Specific objectives of ecological risk assessment for plants. for example. include:

1. determination of the potential for crops to persist and spread in a variety of habitats,
2. discovery of the range of species that can cross-pollinate with various transgenic crops.

Figure 8-2—Risk Assessment Framework for Environmental Introductions



SOURCE: Office of Technology Assessment, 1992.

3. investigation of the ecological performance of hybrid plants produced, and
4. development of protocols making it possible for crop breeders to carry out ecological risk assessments on new transgenic plants in the future.

Box 8-A illustrates the sorts of specific questions that can be asked and answered about plant introductions based on field observations, field experiments, and contained experiments (14).

Risk assessment pertaining to genetically modified (or nonmodified) viruses used in weed biocontrol, as an additional example, would include:

1. information on virus attributes such as virulence, host range, vector specificity, survival, and dispersal characteristics;
2. information on desirable and undesirable virus attributes and on the stability of these attributes;
3. information on the virus' effect on the target weed's genetic stability; and
4. information on the release site and how a variety of ecological variables affect infection, dispersal, population dynamics, and safety (87).

In summary, key features of ecological risk assessments of planned introductions include properties of the introduced organism (not the method by which it was produced) and of the recipient environment. including the demographic characteristics of the organism, the genetic stability and likelihood of gene transfer, and the interactions between the species and the physical and biological parameters of the environment. Scale and frequency of introductions should also be factored into risk assessments. Furthermore, since recapture or recall of introduced organisms usually will not be feasible, assessments should also consider possible means of containment, monitoring, and possible mitigation if adverse consequences occur (74).

Research Needs and Promise of Risk Assessment

The current interest in effective risk assessment of the products of biotechnology has stimulated workshops, conferences, discussions. and articles. More and more frequently. insights from the fields of ecology. population biology, population genetics, and evolution are being recast into the language of risk assessment (31, 50, 52. 62). Additional research needs to be undertaken on a variety of fronts to facilitate risk assessment. For example, a need exists to develop models and use data from field tests to predict the rate of spread of introduced organisms in various situations (54).

Box 8-A—Ecological Risk Assessment Questions

Field observations	Field experiments	Contained experiments
Persistence		
What is the survival of the vegetative parts of the plant under a range of climatic conditions, on soils of different kinds with different categories of drainage? How is perennation affected by the introduced genes? What factors influence plant mortality outside arable fields and how are these influenced by the novel genes? What is the nature of seed dormancy under different environmental conditions, and how does the introduced genetic change influence triggering, duration, and hardiness during dormancy?	What is the fate of seeds sown into a range of plant communities, including other arable crops, forage crops, permanent grasslands, and natural habitats? What is the fate of transplanted seedlings in different habitats? What is the fate of transplanted mature plants (or rootstock) in different vegetation types? How long does experimentally planted seed remain dormant but viable in a range of soil types?	How is pollen viability affected in transgenic plants? How is seed dormancy affected? How do transgenic plants perform in competition experiments with crop plants and with selected native plants?
Spread of the vegetative plant		
What is the seed production of the plant when grown in a crop and in natural vegetation? Is seed production limited by the rate of pollination? What is the germination rate of seeds in soil? What is the mortality of seeds and seedlings in arable soils and beneath native vegetation? What is the phenology of seedling emergence and growth? What are the natural enemies of the seedlings? What is the role of vertebrate and invertebrate herbivores in crop and noncrop habitats? What is the mechanism of seed dispersal? How far are seeds dispersed and how does this vary with environmental conditions? Do the seeds produced by plants grown outside arable fields give rise to a second generation of plants?	What is the vegetative growth rate on different substrates and with different competing species? Is the thinning rule (i.e., density-dependent plant mortality) similar for transgenic and nontransgenic plants? What kind of compensatory growth is exhibited (e.g., gap-filling)?	Is seed size or morphology different in transgenic plants, and how might this affect seed dispersal? Do transgenic plants present greater risks of spread by vegetative fragments?

(continued on next page)

Box 8-A—Ecological Risk Assessment Questions—Conthuecf

Field observations	Field experiments	Contained experiments
If the plant were to prove invasive, at what rate would it spread and which habitats would it occupy?		
Which plant species (if any) are displaced when (and if) the plant is established in natural habitats?		
Which plant species are responsible for the competitive suppression of the plant in different natural habitats?		
Horizontal gene transfer through pollen		
How much pollen is produced?	What is the fate of labeled pollen?	Which plant species allow pollen germination on their stigmas?
What is the phenology of pollen production and what is the phenology of stigma receptivity of other plant species growing in the neighborhood of crops (i.e., within 500-1,000 m)?	How much pollen reaches the stigmas of other wild plants under different conditions?	How is pollen dispersal affected in transgenic plants?
Over what distance is pollen dispersed under different meteorological conditions?	Which insects carry the pollen?	Which plant species form viable, hybrid seed and at what rate is this seed produced?
Which is the pollen deposited, on which species, and in what numbers?	How far away from the crop can an individual, potted crop plant be pollinated and how does the rate of pollination fall off with distance under a range of habitat conditions?	What is the germination rate of hybrid seed?
Where is the pollen deposited, on which species, and in what numbers?	What plants make the most efficient 'pollen barriers' for the construction of guard rows; is it nontransgenic members of the same species or plants that form physical barriers to pollen flow or to insect flight?	What phenotypes are exhibited by hybrid individuals?
What is the geographic distribution of closely related wild plants in the vicinity of centres of crop cultivation and what is their small-scale (100's m) distribution as weeds within arable fields and on land adjoining field foundaries?		What is the performance of hybrid plants in competition experiments with crop plants and with selected native plants?
What natural habitats are found within 1,000 m of arable fields, in those areas where the crops are grown, and what flora is supported by these habitats?		What is the nature of perennation and vegetative dormancy in hybrid and transgenic plants?

SOURCE: Michael J. Crawley, "The Ecology of Genetically Engineered Organisms: Assessing the Environmental Risks," Introduction of *Genetically Modified Organisms into the Environment,* Harold A. Mooney and Giorgio Bernardi (eds.) (New York, NY: John Wiley and Sons, 1990).

Achieving predictive capabilities in extrapolating from field tests to large-scale introductions is an additional goal. Along with further research, data from field tests and research then can feed into the design of future field tests and large-scale introductions. our scientific understanding pertinent to ecological risk assessment should increase exponentially over the next few years.

This explosion of knowledge not only can improve safety but also the effectiveness of introduced organisms in various habitats. There seems to be general agreement, even among ecologists and environmentalists, that most biotechnology products will not be harmful. However, because uncertainty does exist, for instance, as to which applications might be harmful. reasonable caution and willingness to assess risk are appropriate (76).

Risk assessment prior to introductions is a reasonable and necessary step, consensus dictates. More research can sharpen our powers of prediction and build on an already sol id foundation of information. Eventually, criteria can be developed to match individual cases with appropriate risk categories. In the meantime, as a broader knowledge base is being built, the safety of each introduction needs to be judged, basically, on a case-by-case basis (51). Understanding gained from case studies and other relevant research can be employed in the current transition to risk assessments of large-scale introductions.

Applicability of Diverse Bodies of Knowledge to Assessments of Large-Scale Commercial Release

Introduction

In all approaches to risk assessment, the key question is predictability. Do we have sufficient information to make a reasonable prediction as to what will occur for a particular release'? Can we in fact legitimately draw on knowledge gained from agricultural experience, laboratory tests, past field tests of recombinant DNA-modified organisms, and accumulated knowledge of genetics, microbiology, molecular biologics, and ecology? Are the characteristics of any individual large-scale release *familiar* enough that we can bring such knowledge to bear on the risk assessment'?

Species Introductions

Those interested in the evaluation of risks from biotechnology sometimes turn to the experience base with introduced ''exotics, species accidentally or deliberately released in a completely new environment. Dutch elm disease is often-cited as a consequence of the accidental introduction of a fungus; kudzu vine. running rampant in the South after being brought in as a roadside ground cover, is pointed to as a deliberate introduction gone awry.

One viewpoint holds that species invasions may be useful analogues of planned introductions of genetically engineered species, i.e., an invasion is an invasion. Thus. experience with analyses of key properties of 'successful invaders, as well as of vulnerable environments. theoretically can be brought to bear in evaluating planned introductions (63).

Most scientists agree, however, that invasions by exotics have limited applicability to planned introductions of genetically modified species. For example, introduced exotic plants that have caused problems come with many traits that enhance weediness; whereas genetically modified plants, by contrast. are modified in only a few characteristics (69). The distinction between the introduction of modified genotypes of crop organisms and the introductions of totally new exotics-whether or not they are genetically engineered—is, in fact, generally regarded as an important one (14). Even so. lessons learned as to the ecological parameters of ''invading species' and recipient environments may be useful in categorizing degrees of risk for a specific planned introduction of a recombinant DNA-modified organism. For example, comparisons can be made between the characteristics of such an organism and the characteristics often found in very successful invading species. Habitat characteristics can also be compared to help assess site for vulnerability or resistance to invasion (63).

Agriculture

Perhaps the oldest analogue to planned introductions of genetically modified species is agriculture itself. For much of human history, new forms of crops and domesticated animals have been introduced to the environment. Major crops have been bred by the millions for centuries; all these field tests and commercial releases provide a substantial experience base. Throughout this vast experience, no significant harm to human or animal health has occurred due to these introductions per se, nor have major crop plants become bad weeds. Normal selection procedures have eliminated plants with problems. Furthermore, "recalls" of crop varieties are common under the laws of supply and demand. In short, no evidence exists in the United States that plant breeding leads to ecological problems (6).

The NRC report's call for ● 'familiarity" as a criterion for risk assessment makes drawing on the experience base

Photo credit: Monsanto Co.

Genetically engineered tomato plants are shown being planted by researchers at a Monsanto-leased farm in **Jersey County, IL.**

of agriculture logical for most planned introductions of genetically modified agricultural organisms. A specific example of how the agricultural experience can be applied to biotechnology risk assessment is the 80 years of usage of Bt *(Bacillus thuringiensis* with its toxin) as a natural insecticide; its history of safe use is often regarded as evidence that transferring the gene for a Bt toxin would be environmentally safe (6). The 100-year experience base with vaccines, rhizobial bacteria, and other biological controls provides information applicable to large-scale microbial introductions (20, 29, 62, 90). As a final example, corn breeders have significantly changed the corn genome and have conducted planned introductions into the environment of these modifications for the past 70 years, without negative ecological experience. Breeders have gained experience in protecting the purity of these genomes, calculating the likelihood that the modifications will spread to other plants, deploying the modified genomes, and maximizing their strengths and minimizing their weaknesses (18).

Although there are limitations to the analogy between seed purity and gene transfer to weeds (notably, the risks associated with weed genes contaminating seed for planting crops are quite different from those associated with engineered genes getting into a weed population), this analogy does represent a useful starting point for risk assessment in controlled release.

Although some observers emphasize the novelty of gene combinations that can be brought about through biotechnology, a key difference between traditional crop breeding and the "new biotechnology" is that changes in genomes are more precise using biotechnology. With genetic engineering, one gene is moved at a time; by contrast, huge numbers of genes are recombined in crosses that lead to new plant varieties. It is nonetheless true that ecological effects of a changed phenotype sometimes may not be predictable even with precise changes in genotype (85).

Certainly, risk assessments are needed of individual cases involving particular genes. For example, forage crops such as alfalfa, which are not so dependent on cultivation practices, may have higher—and perhaps problematic—survival capabilities outside of the farm than others (6).

Two of the chief concerns about planned introduction of genetically modified species have no analogs in traditional agriculture. With the exception of some introduced crops that become weeds in tropical countries, crop plants have not invaded natural habitats. Furthermore. no obvious problems have arisen due to transfer of genes from traditionally bred crops to wild plants (14).

Laboratory Testing

Results of laboratory tests have been drawn on by those interested in risk assessment of genetically engineered microorganisms in particular. Various studies of microbial genetics, as well as use of soil microcosms (or laboratory model ecosystems) that mimick the natural environment, have provided useful information.

A great many reported laboratory tests involve investigations of mechanisms and likelihoods of gene transfer. For example, transformation (the uptake of naked DNA into a competent or receptive cell) is a form of gene transfer well understood in the laboratory, but not well described in natural settings. Laboratory records on transduction (the transfer of genes between bacterial strains by virus particles) have led to theoretical models predicting the possibility and frequency of transduction from an introduced genetically modified microorganism to a natural species. Another mechanism of horizontal gene transfer studied in the laboratory is conjugation, the process of genetic exchange between bacterial cells. Finally, transposition, the process by which mobile genetic sequences change positions within a genome can be associated with gene transfer.

Soil microcosms, even with sterile soil, are a feasible way of assessing what kind of gene transfer mechanisms *can* occur in nature; they are therefore a useful tool in risk assessment (38, 70). Research has now been done using more realistic soil microcosms, with the objective of learning more about the impact of conjugation on

introduced genetically modified microorganisms. For example, some experiments have been done using nonsterile soils, in an attempt to produce a closer analogue to nature.

Another set of questions that laboratory tests can help address is related to population biology. Relative fitness of genetically modified microorganisms in the laboratory, for example, pertains directly to establishment and possible spread of introduced organisms in an environment; some information toward quantitative risk assessments can be gained from contained laboratory testing in chemostats (44). Laboratory tests also can help illuminate the role played by various soil environments in successful introductions (93).

Of course, constraints exist on the applicability of laboratory tests, having to do with feasibility and with the impossibility of reproducing the full complexity of a natural environment. Some important parameters relevant to introductions are, for example, the relative fitness of the introduced recombinant DNA-modified organism in the new environment with its multiple dimensions of biological, chemical, and physical features, including competition with other microorganisms; microbial population density, which may vary over time and space; population dynamics; and availability of habitats (5). The dynamic complexity of many such features makes it impossible for a laboratory test to mimic reality completely. Work is beginning on testing for effects such as pathogenicity or toxicity in more realistic multispecies systems or microcosms (26).

Perhaps the principal lessons learned from laboratory research have to do with the potential to work creatively with soil microcosms. The more realistic the soil microcosm used, the higher the predictive value of the laboratory tests is likely to be, particularly where extrapolation from the laboratory to the field is relatively well understood. It has been suggested that mesocosms (larger contained walk-in chambers, the environmental parameters of which can be controlled) could provide more realistic complexity than soil microcosms. This added realism might improve risk assessment (93).

Small-Scale Field Tests

Field tests of conventionally produced crop varieties represent part of a step-wise progression toward full-scale commercialization; the same is true of field tests of recombinant DNA-modified organisms. Initially. new varieties are assessed in a laboratory or greenhouse; then they are observed in small-scale field plots where they are evaluated according to various protocols, statistical

Photo credit: Monsanto Co.

Researchers begin test of tomato plants carrying the Bt toxin gene in test plant.

procedures, and analytical methods. Large-scale tests and commercialization complete the process. Each stage provides information for the next stage (53). For the most part. principles and procedures useful in small-scale field tests are also relevant at the large-scale test and commercialization stages as well (36). Field testing and monitoring constitute ''real world empirical methods' that are important components of risk assessment (23).

Small-scale field tests can be used to elucidate characteristics that will be factored into risk assessments of possible large-scale planned introductions. For example, survival and spread of particular recombinant bacteria in a particular soil environment, as well as efficacy of function and stability of an introduced gene. can be estimated in field tests (1, 3, 47). Field tests also can be used to assess ''invasiveness' of transgenic crops (73). Data from field tests can be integrated into quantitative predictive models of gene flow and gene spread (39).

Field tests also provide agronomically significant information, including data on the expression or performance of the introduced gene and on the overall growth and vigor of the genetically modified plant (64). For example, 1990 field tests of insect-resistant cotton plants have allowed such agronomic traits as yield, fiber length, fiber strength, fiber quality, seed composition, and quality to be evaluated by Monsanto, which is planning for commercial introduction in 1994 or 1995 (28).

Well-designed, well-monitored field tests of increasing scale and complexity also should allow undesirable impacts to be observed while there is still an opportunity to correct them (43). A ''stepwise progression in test

design" is seen as an approach to field trials that will reduce complexity and otherwise benefit later I urge-scale efforts (47). (See box 8- B.) An important stage is expansion from single-site into multisite field testing, which allows sites to undergo different conditions, such as weather, and thus provides information on the variation possible in performance and impact *(73)*. Testing over more than 1 year can provide information on the consistency of measured characteristics such as survival and efficacy. Such information will have significant implications for commercial scale planned introductions. Good. statistically sound experimental design can be important in facilitating effective transitions from the field test to commercial-scale introduction (57). For agronomic and risk assessment purposes. scale-up from field tests is a useful and informative process.

There are, however. a few constraints on the applicability of small-scale field tests to large-scale tests or commercialization. An important one is the emphasis often placed on containment in small-scale field tests involving recombinant DNA-modified organisms. Containment is, of course, the antithesis of uncontained, large-scale introduction (36). Bagging plants, for example, prohibits pollination and, furthermore. would not be feasible at a large-scale (53).

When a product is commercialized. it will be far more widespread in the environment than it was in the days of its field test; many more ''nontarget species will be exposed to it (26). As people increasingly use transgenic plants. the chance for errors will increase because some users may not follow safety procedures (43).

Despite these limitations, field tests are providing the datai about agronomic qualities and risk assessment considerations needed for the design of' large-scale tests and commercialization. Detection and monitoring techniques are improving. A step-by-step progression from individual field tests through multisite field tests to large-scale testing to commercialization is being followed for recombinant DNA-modified organisms as it has been for conventionally produced organisms. without problems. Research still needs to be done to identify important distinctions between small-scale and large-scale tests; this should improve experimental design and efficiency (53).

Deliberations on Field Tests and on Large-Scale Release

Over the past several years. field tests have made important contributions to risk assessments for large-scale release of DNA-modfied organisms. The data from field tests provide the most directly relevant basis for predic-

Box 8-B—Learning by Doing: Successive Field Releases

Crop Genetics International (CGI) is a company that has used a "stepwise progression in test design" as it has moved from an initial field test to later tests. The focus was the delivery of biopesticidal gene products by endophytic bacteria inoculated into seeds. First tested was a bacterial endophyte *(Clavibacter xyli* subsp. cynodontis) genetically modified to produce low levels of the delta-endotoxin of ***Bacillus thuringiensis*** (Bt) subsp. *kurstaki*, and inoculated into corn seed. CGI developed a strategy for multiple risk assessment studies of field releases. The focus of the field release studies was twofold: performance of plants grown from endophyte-inoculated seed; and persistence and spread of the genetically modified strain under different environmental conditions. The first two releases were used to develop a profile of the recombinant strain's behavior in the environment. In 1989, the test design was extended to multiple sites in four States to examine its behavior overdiversified environmental conditions. This **was** the first release to take place in multiple States of a viable microorganism genetically modified to produce a biopesticide. In 1990, a new recombinant strain selected for its activity against the target pest (European corn borer) was incorporated readily into the well-established testing procedures and program, with the objective of determining efficiency. As the study progressed between 1988 and 1990, by agreement with regulators, levels of containment were gradually lowered as data on safety were obtained. In fact, the early tests were specifically designed to address risk assessment issues such that future small-scale introductions could be made with less rigid containment and such that containment requirements could be eliminated in large-scale field tests. Efficacy studies now can be done under reduced containment requirements. Multiple-site field testing of the improved strains is the next logical step toward large-scale tests and commercialization. Stepwise progression of tests is a rational strategy from a company's point of view, as well as from a regulator's point of view.

SOURCE: Stanley J. Kostka, "The Design and Execution of Successive Field Releases of Genetically Engineered Microorganisms," *Biologicd Monitoring of Genetically Engineered Plants and Microbes*D.R. MacKenzie and Suzanne C. Henry (eds.) (International Symposium on the Biosafety Results of Field Tests of Genetically Modified Plants and Microorganisms, Kiawah Island, SC, Nov. 27-30, 1990) (Bethesda, MD: Agriculture Research Institute, 1991), pp. 167-176.

(ion as to the safety of large-scale release, particularly in cases where a small-scale field test is itself scaled-up to a large-scale introduction. Equally important, scientists in many disciplines have been gaining practice through field testing in the process of risk assessment. Now that applications for large-scale release are imminent, researchers familiar with comparable evaluations at a small-scale can begin to integrate their experience and apply it to the new assessment task at hand.

Several recent conferences have helped to define approaches to the risk assessment of large-scale introductions. Commonalities arc emerging, suggesting that a state of readiness for large- scale introductions is in fact being reached.

Several biological principles with implications for assessment of large-scale introductions emerged from the International Symposium on the Biosafety Results of Field Tests of Genetically Modified Plants and Microorganisms (November 27–30, 1990. Kiawah Island. South Carolina). For example:

- The integration of genes into the chromosomes of recombinant DNA-modified organisms has proven to be predictably stable.
- Gene transfer frequencies of recombinant DNA-modified organisms are consistent with patterns recorded for natural populations.
- The frequencies of transposon relocations in recombinant DNA-modified organisms are consistent with those of natural populations.
- Some microorganism detection methods are extremely sensitive. and this contributes to better understanding of the fate of a microorganism in the environment.
- Background microbial populations have been characterized as complex. and thus the release of genetically modified microbes may be insignificant by comparison..

The symposium also highlighted the strong foundation of conventional knowledge in crop improvement, microbial testing. and food processing that is available to support safe commercialization of biotechnology products. Research needs cited included: detection methods, sampling methodologies. monitoring protocols and modeling techniques, and empirical data for improved design and evaluation of experiments (53).

A workshop on transgenic plants conducted by the Maryland Biotechnology Institute and the USEPA Office of Pesticide Programs (June 18–20, 1990) evaluated the human and environmentall impacts that could result from the ‘‘widespread. full scale”use of plants genetically modified to produce a pesticidal substance. Workgroups discussed: 1) studies and information needed for assessment; 2) scientific rationale for determining the occasional need for specialized studies; and 3) availability and test protocols for developing risk assessment information.

The consensus of all groups was that such transgenic plants posed concerns and possible effects that are not unique, and risk assessment issues can be addressed through readily obtainable information on possible effects of the plant or of the pesticidal substance (89).

The USDA-sponsored ‘‘Workshop on Safeguards for Planned Introductions of Transgenic oilsecd Crucifers’ (October 9, 1990, Cornell University’) was held to identify agricultural biosafety issues relevant to oilsecd rape (or canola) as soon as possible. Unlike most crops, oilseed rape has weedy relations in North America. The potential for. and possible results of, gene transfer are therefore of concern. The workshop group agreed that with mill ions of acres planted. gene transfer will occur. Therefore, an ‘‘ecological map’ of wild species was called for, so that the location of field trials could be planned to deliberately minimize proximity and hence possibility for gene transfer. Experimental trials and research were recommended to quantify risks. as were studies of the factors influencing gene transfer potential- i .e.. travel of pollen. effective fertilization, the production of viable seed, and the plant reaching reproductive age and passing on its new set of genes. The group agreed that studies should emphasize the conditions under which transfer and expression of the transferred gene take place. and the consequenses-relative risk—of such events (61). A comparable meeting was held for maize and wheat (Keystone, Colorado, December 6–8, 1990); another is planned for rice.

Summary

A long history of agriculture provides an immense bunk of data relevant to risk assessment: diverse scientific fields contribute principles and knowledge. Data from small-scale field tests of recombinant DNA-modified oganisms not only provide specifics necessary for the evaluation of large-scale counterparts. they also provide a risk assessment testing ground. Each risk assessment of a field test adds to the regulator's experience base in adopting risk assessment methodologies to planned introductions. This learning through experience is a natural part of the evolution of oversight as we move from small-scale to large-scalec introductions.

Commercial Release Issues

A variety of issues relevant to planned introductions of recombinant DNA-modified organisms are receiving heightened attention as large-scale commercial releases become imminent. Principal concerns focus on the fitness of the engineered organism (defined as overall genetic contribution to future generations, usually quantified as number of offspring produced) and its potential to become established as a weed or a pest, the stability of the engineered gene, the potential for gene transfer, and impact on other organisms and the environment. Basically, these concerns are the same ones raised with regard to small-scale field tests of genetically engineered organisms. Large-scale agricultural uses involve large numbers of organisms that are usually less contained than their less numerous counterparts in field trials.

Fitness and Potential to Become Established

For a species to become established in a natural community, its relative fitness must be such that it competes successfully with other species. The lack of weediness on the part of most major crops illustrates a direct contrast between domestication and what is useful for survival in the wild (14. 43). Many traits necessary for successful weediness either have never existed in or have been deliberately bred out of crop plants to maximize productivity in a cultivated setting. One analysis showed that serious weeds tend to have on average 10 to 11 ''weedy characteristics'; crop plants have on average only 5 of these characteristics (42). Thus, the chances of any crop plant simultaneously undergoing five to six relevant gene changes to become a weed are vanishingly small (37).

Features of organisms that ecologists identify with weediness include broad ecological tolerance, ability to exploit an under-utilized resource. or ''readaptation' to a new habitat to which the organism is well-suited and in which controlling biological agents *do not exist* (76). Other characteristics that help to make a plant thrive as a weed include the following:

- rapid growth to a flowering stage,
- continuous seed production as long as growing conditions allow,
- high seed output.
- long-lived seed,
- pollination by wind or unspecialized insects,
- high competitive ability,
- broad environmental tolerance,
- seed dispersal over short and long distances, and
- vegetative persistence and propagation.

The probability of successful establishment of a recombinant DNA-modified organism as compared to its unmodified counterpart will naturally be dependent on the nature and phenotypic expression of the specific genotypic modification made, along with the rest of the organism's phenotype, in relation to these ecological criteria. Different kinds of engineered genes will vary in the degree and nature of their impact on the phenotype of the engineered organism. Also, engineered genes may vary in terms of the conditions under which they will be expressed. For example, if a gene is only induced to be expressed under specialized conditions, then its phenotypic impact will be negligible the rest of the time.

It has been well established from studies of induced mutations that most dramatic phenotypic changes in an organism result in reduced fitness (2, 14). Engineered genes that affect the growth, resource allocation, or some other aspect of an organism may convey added economic value, but may also produce a maladapted plant that is unlikely to survive outside of cultivation. On the other hand. genes that have relatively little effect on the overall phenotype, such as genes induced only on certain occasions for disease or pest resistance, might confer a real fitness advantage, even in natural populations. It is generally assumed that genes for disease resistance present a physiological cost that reduces fitness in the absence of disease, although the importance of that cost has been challenged (7 I). However, sometimes if the gene is not expressed, such costs go down, contributing to its potential long-term persistence.

Assessments of the risks of introduced organisms becoming pests must take these factors into account as well as others. For example, introducing a character into an organism whose ecological properties are otherwise well-known, or taking a particular property associated with terrestrial bacteria and introducing it into another terrestrial bacterium, enables some prediction of how that character might respond in that target ecological setting. Thus, in assessing the potential risk associated with a particular phenotypic modification, the target environment should be considered.

If a species became established as a pest, existing communities would be disrupted; fortunately, the likelihood of either a genetically modified plant or a microorganism becoming a pest is relatively low. Most crop varieties produced through conventional means do not become pests (6). Experiments to date indicate that genetically modified microorganisms in some cases may not persist at significant levels (3) and therefore may

often be unlikely to proliferate and disrupt existing com munities composed of vast numbers and numerous species of microorganisms (19. 86). So for all organisms modified in any way. emphases in risk assessment of microorganisms should be placed on the specific product. Until more is known about consequences of large-scale use of genetically modified plants. a deliberate approach rather than complacency seems warranted.

Gene Stability

The stability of an engineered gene is important to risk assessments of planned introductions of recombinant DNA-modified organisms. A gene that has become a stable component of the transgenic organism is more predictable in its function, expression. and possible mobility than one that has not. one aspect of gene stability is persistence. An engineered gene construct usually consists of several components, all of which must be present and intact for the gene to function. In addition to the structural gene that codes for the desired gene product. a promoter gene is needed for it to be expressed—to be turned ‘‘on’ or ‘‘off. Such constructs maybe broken apart by natural genetic recombination. A promoter separated from its structural gene is useless; the structural gene without the promoter remains unexpressed.

The stability of a particular gene also may be directly influenced by the vector used to introduce it into the engineered organism. Bacterial plasmids or DNA-carrying bodies, are potentially the most mobile of the vectors used to insert genes. Plasmids function by inserting themselves into the bacterial chromosome. carrying an engineered gene along with them. Insertion sites for such plasm ids are nonrandom; they are specific sequences that could be recognized by other plasmids, which may pick up the inserted gene and carry it along to another organism. on the other hand, it also is often true that insertion of a particular plasmid will immunize the cell against insertion of similar plasmids.

Genes directly inserted into chromosomes are more stable than genes carried by plasmids. However, chromosomes are complex structures, and the manner in which particular genes express or recombine is determined by their relative positions on chromosomes. An engineered gene inserted in some parts of the chromosome may be more exposed to recombination than genes on other parts of the chromosome. The relative stability of an engineered gene in a plant species can be increased by inserting it into portions of chromosomes subject to lower levels of recombination.

To summarize. a gene’s stability depends on the nature of the gene itself and on the means of introducing it into the recipient organism. Either of these can be manipulated deliberately to increase stability.

Gene Transfer

Another appropriate focus for risk asessments of planned introduction of recombinant DNA-modified organisms is the possibility) that novel genes may become incorporated into related wild species. Such transfers, it is argued, might lead to harmful bacteria or weeds with an " improved" characteristic such as resistance to pest attack: this might make them more difficult to control. Three key questions to be considered are: What is the probability that a gene will move from an agricultural organism to wild species’? What can be done to lower the probability? What would be the consequences of such gene transfer on agricultural and natural communities<? (37)

The probability of gene transfer from a recombinant DNA-modified organism to a wild relative depends on the introduced organism and the nature of the original gene transfer mechanism. For microorganisms such as bacteria the primary means of genetic transformation is by vectors that, as noted above. are readily incorporated into organisms and mobile between organisms. This opens up the prospect of horizontal transfer of modified genes.

In addition to vector-mediated gene transfers, or transduction, genetic transfer in bacteria can occur by transformation, in which DNA freely existing in the environment is incorporated into living cells; and conjugation, in which DNA is transferred by direct organism to organism contact (27). These mechanisms are well known from in vitro studies of microorganisms under laboratory conditions; indeed, transduction has become a common tool in the introduction of engineered genes into bacteria (55). However, little is known of the properties of these transmission mechanisms in nature (80). Due to the complexity of the bacterial environment, the scope for bacteria to bacteria contact or for mobility of bacteriophages and bacteria are much more restricted in soil than in laboratory culture.

Risk assessment of gene transfer in natural bacteria populations is also problematic because species composition and potential for gene transfer among species is poorly understood. Only a small fraction of the bacterial species growing in soil occur in sufficient numbers to be recognized by standard isolation techniques (48). It has been argued that slow-growing organisms occur in sufficiently low numbers that their potential interactions and any subsequent possible risks are negligible.

On the bright side, a number of recently developed techniques exist that can greatly facilitate studies of bacterial interactions in natural substrates (48), including flow cytometry (a technique that involves the use of laser-activated fluorescence of stained particles) and polymerase chain reaction (PCR) (65), involving the amplification of a particular gene contained at low concentration in soil to sufficiently high concentrations that it can be detected by standard DNA analysis. PCR can be used to monitor the movements of introduced genes in natural substrates (79). This allows the population dynamics of the engineered organism to be more closely monitored, the transmission of the engineered gene to background organisms to be quantified, and potential risks to be evaluated. Also, the introduced population can be "tagged' with a specific but nonfunctional DNA sequence such that the growth or decline of that population in the soil can be monitored independently of the engineered gene(s).

Actual probabilities of gene transfer of various kinds among microorganisms are still being researched. Although differing opinions certainly exist, one school of thought is that the order of magnitude of microorganisms present in the natural community, and the probable frequency with which they exchange genes, renders the potential impact of most recombinant genes being transferred relatively low.

For higher organisms. vector-mediated transfer of engineered genes is not a major concern. For example, a widely used vector for dicotyledormus plants, *Agrobacterium tumefaciens* (crown gall virus) can be readily screened out of transformed organisms before they are released. Furthermore. for many important crop species, notably cereal crops, vectors for gene transfer are not used: rather ballistic incorporation of genetic material into tissue-cultured cells (using '"gene guns') is the method currently in development. Using this method there is no chance of vector-mediated gene transfer. This leaves gene transfer through hybridization of crops and reproductively compatible (i. e., closely related) weeds as a possibility.

In higher plants, the main risk associated with gene transfer from transgenics into surrounding populations is. in fact, that of hybridization. Modified genes potentially could be transferred from transgenic plants and incorporated into the genome of a weedy species through introgressive hybridization, whereby genes are transmitted through pollen in sexual reproduction. However, working against this possibility are limited viaility of pollen, distance and physical barriers to pollination. genetic dissimilarities (i. e., incompatible fertilization processes), and failure to produce viable, fertile offspring.

Most crops grown on a large scale in temperate regions, such as corn and wheat, are grown outside of their geographic region of origin; consequently there typically are no related weed species growing in association with them. Therefore, for most crop species in the United States, pollen-mediated transfer of modified genesis only of theoretical concern. However, there are several important crop species for which closely related weed species have become introduced. Specifically. many crops in the family Brassicaceae. such as canola (oil-seed rape) and radishes, have co-occurring weedy relatives (21). Sunflowers had their center of origin in the United States and have related weedy species here as well.

Most major crop species originated in what arnow regarded as developing countries. For example, corn was developed in Central America, wheat was first cultivated in the Middle East, rice in Southeast Asia. and potatoes in South America (77). Consequently, introduction of genetically engineered crops into such regions should be handled with particular attention to the probability of gene transfer into background populations.

Additional concern focuses on the potential impact of introduced genes on the genetic structure of natural populations of plants related to important crop species. These populations represent the genetic heritage of the crop and are an irreplaceable reservoir of diverse genetic variation that may be needed in future development of the crop (8). If, because of a novel gene effect, one strain or lineage became a super weed it might outcompete and therefore eliminate other lineages; genetic variation potentially useful for crop development could be lost. More generally, biodiversity is intrinsically valued by many (12).

Pollen-mediated transfer of novel genes from crops into related weeds might also result in weeds becoming similar to the crop species. A number of well-known instances exist where selection pressures exerted by traditional agronomic practices have caused weedy species to evolve to resemble the crop species. Such weeds cannot be eliminated by standard control practices (4). Thus, weeds are capable of a wide range of genetic adaptation even without the introduction of novel genes. Although there could clearly be problems associated with potential gene transfer from transgenic plants into weed populations. there is also a large experience base in agricultural and natural populations on which to draw for predictions in this area.

A great deal is known about pollen transfer in plants **(35)** and associated Likelihoods of gene transfer. In the past few years, there has been a growing interest in tracking pollen in natural populations through ''paternity analysis, " a technique directly analogous to human paternity analysis (58, 82). The development of such approaches provides a useful means of evaluating the potential spread of modified genes, as well as a means of testing the efficacy of various measures to prevent pollen spread into wild relatives.

Gene flow in many crop species has also been studied extensively in order to determine necessary distances for genetic isolation of different plots to reduce genetic contamination of seed crops in conventional agriculture. For example, genetic contamination of seed in plantations of conifers can reach levels of 30 to 50 percent and is an extensively studied problem (78). A review of gene transfer from corn to related species concluded that the prospects for introgressive hybridization in corn were limited (17). However. it is unwise to dismiss completely consideration of gene transfer because genes transmitted at low levels could be rapidly enhanced through natural selection if they confer an advantage to their recipients. A study of hybridization among six different rice cultivars developed through conventional agriculture and the related weed *red* rice (Oryza sativa L.) found widely varying rates of hybridization with the different cultivars. The hybrids generally showed evidence of convergence towards the crop, thus opening the possibility of generating a particularly noxious weed that closely resembles the crop (49).

For specific applications of biotechnology, it is possible to articulate potential risks of gene transfer and evaluate their probability. Furthermore, long-standing agricultural practices (e. g., isolation of crops for seed certification) can be useful in managing this risk. For the few U.S. crops with weedy relatives (i.e., canola), and for other countries where crops have multiple related species, careful risk assessment should lead to reasonable risk management. It is important to remember that successful cross hybridization is in fact a complex multistep process and does not usually lead to viable, fertile hybrids. unless the species are closely related.

Evolutionary Pressures Placed on Other Organisms

Evolutionary pressures on indigenous organisms can arise in several ways. Novel organisms in a biotic community may provide new levels of competitive interactions; they may impose direct selection pressures on the native organisms; they may also enhance one species at the expense of others. Thus the assessment of risks (and benefits) associated with the planned introduction of recombinant DNA-modified organisms must consider the engineered organisms' probable interactions with the target biotic community.

Many such interactions occur in convolution of a cultivated species and its associated pathogens. pests. and weeds. One interaction that should be beneficial in terms of controlling crop pathogens involves a pathogen's response to "resistance factors." Factors conferring resistance to pathogens can be conventionally bred or genetically engineered into plants. It is well established that the introduction of pathogen resistance factors imposes selection pressures on pathogens to overcome these factors by evolving greater virulence (34). Using conventional breeding methods, it can take longer to introduce a resistance factor into a crop species than it does for pathogens to respond. Genetic engineering promises greatly to reduce the time frame for introducing resistance factors. This ''buys" the crop some lead time before the pathogen evolves a response.

Strong selection pressures also are exerted on pest species to evolve counter measures to control technologies. The use of *Bacillus thurigiensis (* Bt. for example, is an effective means of controlling insect pests that could become overutilized and thus rendered ineffective. The bacterium itself often is used in broadcast spray applications to control insect pests, and the gene for toxic agents in *Bacillus* thuringiensis has been cloned. The gene now is being incorporated into crop species in field tests. This will exert even stronger selection pressure on insect pests. Several approaches may help to diminish selection pressure and thus slow down the rate of evolution of resistance. (See ch. 6.) It may be possible, for example, to introduce the Bt gene in such a way that it is only turned on during certain stages of development, only in certain parts of the plant. or only at times of insect attack, thus decreasing its impact. Scientists from several agricultural companies have formed a Bt **resis**tance ''club' to discuss how to slow the evolution of resistance to Bt.

Another concern is that use of genetically engineered crops for herbicide resistance may result in overuse of specific herbicides and thus impose strong selection on weeds to evolve resistance to those herbicides. For example. if even ''environmenttally friendly" herbicides are overused in conjunction with transgenic monoculture, weeds might evolve resistance fairly rapidly. This may lead to a "desperate" use of far more damaging herbi-

cides. Management strategies for slowing the development of resistance may be needed. (See ch. 6.)

The convolution of a cultivated species and its associated pathogens and weeds is a quite predictable process if one genetic locus for one resistance factor is considered. The sequential introduction of resistance factors in a crop species ultimately can lead to the so-called ''gene for gene' condition in which each gene for some resistance factor in the host is matched by a gene for virulence in the pathogen. One way to break this cycle is simultaneously to introduce multiple resistance factors, thus impeding the pest's evolutionary response. Similarly, different resistance factors might be cycled from year to year so that the pest never fully responds to any one resistance factor (34). The use of genetic engineering techniques could greatly facilitate such strategies because it provides a tool for rapid generation of new lines containing different combinations of resistance factors.

Monitoring

Assessing the potential risks of environmental introductions of recombinant DNA-modified organisms, and evaluating how best to manage these risks, entails spatial and temporal monitoring of the organisms and of their introduced genes. Monitoring contributes to risk assessment and management in two ways. First. in a specific situation, it tracks indicators of gene transfer or spread of introduced organisms so that action can be taken if needed. Beyond this, monitoring adds to our database, so that risk assessments of subsequent introductions are even more accurate. Monitoring of field tests can provide information pertinent to subsequent field tests and to large-scale introductions. For example, presence or amount of gene transfer from transgenic crops to related or nonrelated weedy species could be estimated from monitoring species surrounding a test field containing a recombinant DNA-modified crop. These data can be used in future field tests or large-scale introductions involving similar crop/weed complexes. Monitoring also can help elucidate any spread of introduced microorganisms. As the ecology of their spread is understood more fully, risk assessments of new introductions can be improved. Thus, monitoring has an important role to play in the natural evolution of science-based. risk-based regulatory oversight. Highly sensitive monitoring techniques are developing rapidly. (See box 8-C.)

The following is an example of the kind of data that the Animal and Plant Health Inspection Service (APHIS) can require from monitoring (in this case recombinant entomocidal or insect-killing bacteria were field tested). Required monitoring provided data on:

1. plant colonization by the recombinant bacteria at 4 weeks after inoculation;
2. colonization of all plant parts by the recombinant bacteria monthly for 4 months;
3. dispersal, natural and mechanical, in the field of the recombinant bacteria after 60 days;
4. presence in run-off water of the recombinant bacteria;
5. presence in soil of recombinant bacteria populations;
6. effect on crop yield of the recombinant bacteria;
7. effect on crop residue decomposition of the recombinant bacteria;
8. effect on vesicular-arbuscular mycorrhizae of the recombinant bacteria 3 and 6 weeks after planting; and
9. effects of the recombinant bacteria on saprophytic gram-negative bacteria in the phylloplane.

Other points of interest needed to be addressed through the ability to track the recombinant bacteria, as well (22).

The monitoring data collected enabled APHIS to assess patterns of the spread of the recombinant bacteria on the targeted plant and its various parts, the dispersal of the bacteria in the field water and soil, effects of the bacteria on crop yield and decomposition, and the effects of the recombinant bacteria on mycorrhizae and other plant bacteria. In short, required monitoring of plants and soil contributed directly to understanding of dispersal and effects of the recombinant bacteria.

Plants generally are easier to monitor than microorganisms. As techniques for monitoring improve, field test data and, soon, large-scale test data will improve our knowledge of survival and spread of recombinant DNA-modified organisms and their genes. thus aiding us in reasoned risk assessment and management.

Research Needs

For the past two decades, basic research in molecular biology has generated many novel scientific insights and products. As a result of strong government support for such research, we have reached a point where the planned introduction of recombinant DNA-modified organisms is a reality. However, the fields of ecology and evolutionary biology, which can provide the kind of information and expertise needed to predict the impacts of planned introductions, have enjoyed less support. Fortunately, ecologists are now taking a leading role in defining a research

Box 8-C—Monitoring Microorganisms

Detection and tracking (monitoring) of recombinant DNA-modified organisms and their genes makes possible quantification of persistence or spread. Highly sensitive new techniques, among them polymerase chain reaction (PCR) and antibodies, are being utilized to contribute to the efficacy of monitoring. Data resulting from monitoring in turn contribute to the knowledge base on which risk assessments of prospective small-scale and large-scale introductions can be based. In fact, regulatory agencies' request that certain parameters be monitored in field tests allows them to fine tune upcoming assessments of large-scale applications, and to make plans for their management.

The first approved environmental introduction of a living genetically modified soil-borne bacterium in the United States, in fact, had as its goal monitoring of the bacterium's population dynamics, persistence, and movement through the soil. The genes "lac Z" and "lac Y" were engineered into a root-colonizing fluorescent pseudomonas (P. *aureofaciens),* part of a bacterial group that often promotes plant growth and protects against some plant diseases. The added genes allow the bacterium to use lactose as a source of carbon and energy and result in readily discernible deep blue bacterial colonies on a petri dish, thus providing an excellent monitoring tool. Scientists from Clemson University and Monsanto studied bacterial spread, population dynamics, and persistence over three crop cycles (19 months) in a wheat field and found similar values for both the modified and the nonmodified strains. Both strains declined to below detectable limits 38 weeks after inoculation. Also monitored were the foliar tissue of the first winter wheat crop analyzed 3 weeks before harvest and found not to have either strain present; and native soil bacteria, to which the Iac Z and Iac Y genes were not found to have transferred. The study's multifaceted sampling design, use of new techniques such as chromosomal DNA fingerprint patterns, presence of a control in the form of a nonengineered strain, and followup over three crop cycles set good examples for thorough monitoring studies in other situations (45). This work also is noteworthy as the first study analyzing frequency of genetic exchange in the environment of genes inserted into bacterial chromosomes rather than plasmids. This "success" of the chromosomal approach has implications for scientific management of gene transfer in microorganisms.

In future monitoring studies, the transgenic organism or the inserted gene itself might be tracked by a nucleic acid probe for a specific DNA sequence; as well as by selective media for metabolic characteristics or by antibodies to a characteristic antigen. Some tracking techniques require that bacteria be isolated and grown in the laboratory, but others are being developed that can analyze bacterial DNA as isolated from environmental samples, a capability useful in estimating the population of the introduced organisms. Still other techniques, including pulsed field electrophoresis, can be used to analyze total DNA in a simple community and possibly to then quantify different members from the sample. In communities that are more complex, higher resolution is needed and probes maybe necessary. In such cases, antibodies may give a great deal of information by tracking phenotype through detection of proteins present (19). Polymerase chain reaction methodology is an innovative technique that can be used essentially to "magnify" sensitivity of detection. Flow cytometry, a cell-sorting technique, may also have some application to monitoring.

SOURCE: Philip C. Kearney and James M. Tiedje, "Methods Used to Track Introduced Genetically Engineered Organisms," *Biiotechno/ogy for Crop Protection,* Paul Hedin, Julius Menn, Robert Hollingworth (ads.) (Washington, DC: American Chemical Society, 1988).

agendna to respond to a variety of social needs, including the planned introduction of' recombinant DNA-modified organisms (85). Since introduced species or their genes may be incorporated into natural biota, over time. a similar agenda is needed for evolutionary biology to assess the likelihood of propagation and persistence.

The likelihood of an introduced organism becoming established. competing with other organisms. spreading. exchanging genes with members of other species. indirectly affecting nontarget species, or changing over evolutionary time all need to be predicted in risk assessment. A number of fields in biology are already making contributions to these predictive capabilities. However. funding for further research is needed. (See box 8-D.)

Development of mechanisms for effective coommunication between fields is critical to meeting research needs associated with the planned introduction of recombinant DNA-modified organisms. It has been noted that interdisciplinary research is critical for the development of risk assessment and risk management pertinent to planned introductions (92). In particular. the gap between ecology and molecular biology needs to be spanned. Scientists in both areas need to be trained or encouraged to be more aware of each other's fields.

130x 8-D—Relevant Research Fields

Community Ecology

Community ecology is the study of interactions of populations of different species in a given habitat. Interspecific competition, predation, and other interactions are the province of this field. Modern community ecology is an experimental field; however, most experimental studies are limited in scope to consideration of two, or at most three interacting species. Larger experiments focusing on more realistically complex interactions, and desirable predictability of response to perturbation, will require more research. Ecological systems research on topics such as nutrient cycling can provide relevant information as well.

Population Ecology

Population ecology is the study of the dynamics and growth of populations. Such studies may emphasize properties of the species itself, such as fecundity or mortality rates, or they may emphasize effects of environmental or biotic interactions. There is a growing trend to incorporate population ecology into conservation biology. Analysis of life history can be used to determine which stages (e.g., seedling establishment versus adult survivorship) are limiting to population growth. Such analyses of sensitivity in population dynamics (9) could be useful in risk assessment of ecological impacts of recombinant DNA-modified organisms.

Population Genetics

Population genetics is the analytical study of properties of genes and changes in gene frequency over time. The mechanism by which genes are transmitted from one generation to the next and the relationship between particular genes and fitness are key to this field. This field is distinctive among biological fields because of its sophisticated theoretical framework. The theory enables some level of prediction about the behavior of genes in populations, but more emphasis on empirical studies is needed to generate useful predictive models of gene change.

Evolutionary Biology

One way to encourage empirical work in population genetics would be to place more emphasis on research in evolutionary biology. Changes over time in genetic structure—and consequent phenotypes-of populations are foci of evolutionary theory. Emphasis on dynamics of change predisposes the field towards questions of relative Spread of genes and impact of phemotypes in an ecosystem over time; these are questions that are relevant to risk assessment of planned introductions.

Systematic

The field of systematic encompasses analysis of variation of different levels of taxonomic organization. Although the ultimate goal of such analysis is taxonomic classification, this field is increasing in importance in analysis and monitoring of biotic diversity. This field could contribute to risk assessment through analysis of species relationships and species ranges to evaluate the probabilities of hybridization.

Mathamatical Modeling

Mathematical modeling entails construction of a mathematical framework to describe a process and predict outcomes from that process. Modeling has been an effective approach in risk assessment and strategic planning in agriculture, For example, models have demonstrated that allowing the existence of marginal populations of pests lets them serve as reservoirs for genes that confer susceptibility to pesticides and other means of control, such populations therefore can beneficially slow the rate of evolution of resistance (34). This seemingly counterintuitive result contraindicates a straightforward program of eradication.

Risk Assessment Methodologies

Risk assessment involves the ranking of probable outcomes from possible events. As such, in order to rank risks, one needs to first define the risks of a given practice. Development of risk assessment methodologies is an ongoing practice, and practitioners must always be ready to adapt to new problems as they arise in different situations, such as commercialization of diverse crops in a variety of environments.

SOURCE: Office of Technology Assessment, 1992.

More communication between scientists involved in basic research and applied research is also needed. Just one example is the need for communication and interaction between plant-resistance breeders and evolutionary biologists (33). Another example would be communication between farm management systems research and ecology. Many people who work in basic research are in part motivated by applied concerns. However, it does little good to generate insights on an applied problem unless there are lines of communication whereby the results of those insights are incorporated to solve the problem. Questions regarding applied problems also need to be articulated to basic researchers.

RISK MANAGEMENT

Genetically modified organisms introduced into the environment do not present us with radically novel problems. Furthermore, we have a sufficient enough base of technical knowledge and risk assessment methodologies that we can make reasonable, science-based assessments of the likely impacts of individual proposed introductions. The concerns raised do not need to paralyze agricultural progress based on biotechnology. These concerns can be respected, weighed, and addressed as necessary through science-based regulations and scientific and agronomic methods of managing risk.

Design of Science-Based Regulation

The 1986 Coordinated Framework (5 I FR 23302-23393, 1986). the more recent scope document (55 FR 147, 3118. 1990). **and other** reports attempt to create a technically sound context for biotechnology oversight. (See ch. 7.) Reviews of field trials to date have been based on technical issues of risk reduction. Technically sound evaluations of safety can provide principles for regulation and oversight. Agencies receiving proposals can add specific stipulations for risk management (66). A variety of scientific fields ranging from molecular genetics to ecology need to be brought to bear on the design or performance of oversight. As research progresses. predictability about risks and insights as to how they should be managed will improve.

The imminence of large-scale introductions underscores the need for clarification of how risk will be managed in various situations. Identification of issues. development of policy, and structure for large-scale tests and commericializations, along with modifications of the approval process for small-scale field tests, are all being requested from regulatory agencies, who are themselves grappling with the issues involved (36).

Generic v. Case-by-Case Approach

Extrapolation of results of risk assessment from one site to another still needs refining; this has ramifications for multisite, large-scale introductions. Many believe that ‘evaluation of risks must be specific to the particular application. However, attempts have been and doubtless will be made to associate individual cases with appropriate categories of risk and to manage them accordingly (51).

One key issue in the approach to risk management in planned introductions of recombinant DNA-modified organisms is whether to use a case-by-case analysis approval process or a process built on generic categories. Some, looking at the large number of applications coming down the pipeline, advocate a shift from the current case-by-case review of experiments toward more of a generic approach. Possible strategies under this approach include categorical exemptions, licensing certain categories of tests. licensing individual scientists. or delegating authority to institutions (53). Others fully expect large-scale tests and commercialization. in particular, to be reviewed on a case-by-case basis. but they do encourage the rapid appearance of protocols or some other form of guidance so that safe and effective products can be developed (36).

Advocates of a case-by-case approach point to its flexibility. As different cases arise, each can be dealt with in a manner appropriate to its nature; no one set of rules and regulations, it is argued, will cover all of the many and varied applications of biotechnologgy.

Nonetheless, over time, as our experience and research base grows it is likely that some generic approaches to certain sorts of introductions in certain sorts of environments will emerge. The criteria by which these generic approaches are defined (some requiring more attention than others) will themselves change over time (74). These developments were anticipated in the ESA report (85), which made a significant step toward scaling risks. Eventually. generic categorizations of likely risk are probable, yet each case will need to be double-checked for any idiosyncratic particularity that could trigger more focused review. It is important for the successful application of biotechnology to agriculture that sufficient long-term flexibility is built into the regulatory and oversight system

so that risk management can evolve based on improved understanding.

Relative Risks Compared to Traditional Practices

Risk management involves the weighing of costs and benefits. To put planned introductions in context, their risks could be compared to risks of traditional practices in agriculture and society. For example, risks today are associated with the widespread use of chemical pesticides; accumulation of nonbiodegradable materials; toxic wastes; agricultural practices giving rise to genetic uniformity in farm animals and crops, with loss of biological diversity; and ''natural biological calamities, ' such as the current epidemic of AIDS. Not only are risks of planned introductions put into perspective by these nonbiotechnology-related problems, but biotechnology itself may help to solve some of them. For example, biotechnology can provide alternatives to chemical pesticides, assist in the degradation of toxic wastes, provide alternatives to selective inbreeding, and contribute to development of diagnostics and vaccines for AIDs and other illnesses (74).

On a more specific level of cost/benefit comparisons, new biotechnology techniques can be compared to those associated with traditional biotechnologies. (See table 8-1 for one view of such a comparison.) Certainly controversy exists—for instance, over the relative predictability of the ecological behavior of the phenotypes of transgenic organisms even when genotype changes are precise and well-understood. On the other hand, conventional breeding changes many genes simultaneously, with consequent multiple phenotypic changes. The newer, more precise techniques may actually show up well in the comparison.

Cost-Benefit Analyses

Risk management includes the weighing of risks or of actual costs on the one hand against benefits on the other, and then trying to achieve a reasonable balance (74). Agricultural biotechnology has potential to create positive benefits for agriculture. horticulture, range management, and forestry in the 21st century (43) if it is not stalled in its developmental stages; on the other hand, it is to no one's best interests to proceed without attention to identifying and minimizing any likelihood of risks. An appropriate balance is necessary.

In a time when the expansion potential of land for agriculture is small, when labor is expensive, and when additional use of chemicals in agriculture generally is regarded as a negative, the possible exploitation of new capabilities and new information through new technologies cannot be ignored. Thus, regulations that are not science-based could exact a very real ''cost, that of not introducing an innovative, promising product.

Small-Scale v. Large-Scale Issues

As agricultural biotechnology nears the commercialization stage, risk management must take into account a number of realities, as was mentioned in the previous chapter. For example, large plots at a number of locations are needed to test a recombinant corn line. This testing needs to be done within I to 2 years of the creation of the recombinant line for a company to stay competitive in the development of new varieties. Furthermore, many hybrids will be undergoing evaluation at the same time; several of these may contain the same recombinant gene and several recombinant genes might be examined simultaneously. In short, if the recombinant material goes

Table 8-l—Comparison of Traditional and Developing Biotechnology

Characteristics	Organismal	Cellular	Molecular
Processes	Breeding	Culture - Cell - Anther - Embryo	rDNA
	Selection	Regeneration	
	Mutation	Fusion	
Control over changes	Random	Semi-random	Directed, precise
Primary changes	Unknown	Semi-known	Known
Number of variants needed	Large	Intermediate	Small, in vitro selection methods
Species restriction	Mainly within	Within & across	Within & across
Familiarity	Very high	Intermediate	Low but expanding
Ability to ask and answer risk questions	Low	Intermediate	High
Containment	Dependent on organism and independent of method; established procedures for domesticated organisms.		

SOURCE: R.W.F. Hardy, '(Large-Scale Field Testing and Commercialization: Thoughts on Issues," *Biological Monitoring of Genetically Engineered Plants and Microbes,* D.R. MacKenzie and S.C, Henry (ads.) (Bethesda, MD: Agriculture Research Institute, 1991),

successfully and quickly through testing, the breeder will soon work to combine it with other useful traits, in different genetic backgrounds, as part of genetic improvement. Large numbers of new lines will emerge from the integration of recombinant genes into conventional breeding programs so that new hybrids can be tested and commercialized.

Specific recommendations for risk management of the transition to large-scale could include: I) making geographic maps of crop relatives and placing them in an accessible database, and 2) modifying the process for approving small-scale introductions based on experience base or familiarity (36). Marshaling evidence from experiences in agriculture, laboratory tests, introductions, field tests, and current, ongoing research will make possible reasoned risk assessment and management.

SCIENTIFIC METHODS OF MANAGING RISK

The power and precision of biotechnology can be harnessed for risk management itself. Controlling the spread of introduced genes through the manner in which they are introduced is one example. Risk management can be greatly aided by using supplementary transferred genes to ensure that the ensuing recombinant DNA-modified organism only functions on certain occasions, under certain environmental conditions, or for a finite period of time. The genetic modification can be designed to: 1) constrain the potential for gene transfer (increasing the "containment' of the gene within the organism into which it was inserted), and 2) maximize its key activity while **minimizing effects** in the recipient environment (60). Mechanisms for fine-tuned technical control of this sort still are being developed; a few approaches are described briefly here. In general. in addition to turning the gene on or off under certain conditions, several approaches to containment could be considered: ''autodestruct'" mechanisms (e. g., suicide genes), engineering genes such that the host has diminished survival (as through defective regulation of metabolism), and decreasing chances of horizontal gene transfer to other organisms (as through reducing the stability or ease of inheritance of the introduced genes) (19).

Promoters Turned On or Off by Specific Stimuli

One way to limit the effect of the engineered gene itself is to attach it to a promoter that only allows expression under certain conditions (83). When a gene is not being expressed, the physiological expenditure associated with expression of the gene can be allocated to other purposes. This maintains the "efficiency" of the organism and keeps the impact of the gene's phenotype to a minimum. For example, some genes are only expressed when triggered or induced (usually through a ''promoter' gene) by a certain chemical, such as a herbicide, or in the event of local disturbance of tissue, such as a wound response resulting from chewing by insects. A gene for some form of pest resistance attached to such an ''inducible promoter' gene would have little phenotypic impact except in the presence of a pest. This is a realistic strategy with diverse applications, some of which already have been field tested. For example, a field test was conducted by Iowa State University to assess whether or not transgenic tobacco plants would respond to insect attack by turning on an inserted gene. Plants often can respond to insect attack by activating genes coding for defensive compounds. Such compounds may, for instance, block the digestive system of insects, reducing their leaf consumption. A marker gene—one used to trace the success of the recombination experiment—(chloramphenicol acetyl transferase, CAT). modified from proteinase inhibitor II genes in the tomato family, was put into tobacco to determine levels of its activation by insects under actual field conditions. Upon insect attack on foliage, the transgenic plants showed induction of the transferred proteinase inhibitor genes. This has positive implications for using the wound-inducible inhibitor promoter in biological control of insect-caused foliage damage. The potential exists for a well-managed. efficient system, in which the inserted genes function only on an as-needed basis (83).

Suicide Genes

When it is important that particular recombinant DNA-modified organisms not establish viable populations, a mechanism that has been proposed for their containment is to include, along with the desired gene, a "suicide" gene that will sufficiently cripple the organism that it will not survive beyond its intended use. The suicide gene may, for example. prompt a metabolic pathway resulting in death of the cell in the presence of a specific external cue (44, 70). Another approach to containment is to introduce mutations that inactivate the transgenic organism's ability to synthesize necessary aromatic amino acids or other key metabolic pathways of the cell (19).

Alternatively. a "kill" gene can be inserted to be expressed constitutively — all the time-unless a ''protection" gene is turned on by the same promoter gene that causes expression of the key functional gene. That

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promoter can be geared to respond to some signal from the environment, such as temperature or presence of a pollutant chemical. For instance, if a protection gene for a vaccine strain is only activated above temperatures of 30 “C.. the vaccine organism will express the kill gene and die if it passes out of the host’s body (19).

The advantages of a “suicide” strategy are straightforward. Existing experimental data indicate that genetically modified microorganisms introduced into the environment usually fail to establish viable populations unless the numbers of introduced organisms are very large. To accomplish a useful effect, as in agricultural treatments or environmental clean-up, planned introductions of microorganisms generally will require inocula of large populations. Once the goal of the planned introduction has been met, a trigger factor to set off the suicide gene can be introduced that will leave behind only a small fraction of the introduced population, which may then be at too low a frequency to sustain itself.

Suicide genes are most frequently suggested for containment of microorganisms; their feasibility in plants has been questioned. With plants’ complicated physiology. difficulties could exist, for instance, in triggering the action of specific genes by any environmental cue other than some deliberate applied chemical, such as a herbicide (37). Overall, the potential effectiveness of suicide genes at this point is controversial (25). One key problem with the use of suicide genes is that natural selection would encourage the evolution of genetically based mechanisms counteracting the suicide effect.

Prevention of Gene Transfer

In the case of transgenic plants, concerns exist about the possible transfer of engineered genes to neighboring weedy populations of related species. One way to prevent gene transfer through pollen would be to shut down pollen production in the transgenic plant. This can be accomplished by introducing a male-sterility factor into the plant along with the desired trait. The use of naturally occurring male-sterility mutants has been a significant tool in traditional plant breeding. Quite recently, genes for male sterility have been cloned and reintroduced into several plant species, including canola (56). These genes were expressed in the transgenic plants and hence brought about male sterility. This strategy has a great deal of promise and currently is feasible. Its application to canola is especially pertinent because that species is among the most likel y to effect vector gene transfer to related species in North America.

For leafy crops (e.g., spinach) or root crops (e. g., sugar beets), male sterility would not be problematic. In fact, it has been suggested that male sterility used in timber tree plantations would channel more of a tree’s resources to board feet production, in lieu of reproduction. Some crops (e. g., cereals), however, require pollination, so that mixed varietal plantings of male sterile transgenic plants and male fertile. untransformed varieties could be needed (37).

Several strategies seem to have potential to decrease the risks associated with gene transfer between microorganisms. For example, a protection gene might be inserted far away from a kill gene. which itself is close to the desired gene being introduced to a host; then, if the functional gene happens to be transferred, the new recipient microorganism also would receive the kill gene, without the protection gene. Another approach might be to insert a gene for a particular active nuclease so that when a cell dies, its DNA—including the introduced fragment-released after death will have been significantly reduced. A variety of ways of inserting defects that would disrupt the host’s mobilization and conjugation systems could also cut down significantly on horizontal gene transfer (19). Engineering changes into a chromosome rather than a plasmid may decrease the likelihood of gene transfer between microorganisms; this approach also is being explored (45, 48).

Combinations of Genes

As the number of genes involved in a desired effect goes up. so does the possibility that that effect will be lost in the next and subsequent generations because of natural recombination. Thus, a possible strategy for decreasing the long-term probability of establishment of an engineered genetic effect would be to have the desired effect depend on the interaction among several separate genes.

AGRONOMIC METHODS OF MANAGING RISK

Physical Barriers

Complete containment was the preferred method of controlling risk when genetic engineering was introduced on a small scale. Examples of physical containment are “boundary strips” in the form of fences or hedgerows that can trap some large percentage of pollen. particularly that dispersed by wind. This might, however, be unfeasible to install or cause unwanted shade (37). Overall.

Photo credit: Grant Heilman, Inc.

A traditional approach to isolation of plants is to spatially separate desired plants from other plants. Similar guidelines for spatial segregation have been applied to transgenic plants as well.

a complete containment strategy has extremely limited applicability beyond small field tests. Once an organism has been placed in the field in the numbers required by agricultural production, it is likely to be exposed to a variety of biotic interactions beyond the control of reasonable physical barriers.

Spatial Barriers

The traditional approach to isolation of plants genetically improved through conventional breeding, usually for the purpose of generating a seed crop, is to isolate spatially the desired plants from other plants. Similar guidelines for spatial segregation have been applied to transgenic plants as well (64). Certainly this is feasible at the small field trial stage, and could be effective in an experimental setting to evaluate the properties of the organism as a potential pest. Some spatial separation may be feasible at the large-scale test stage, as well. Another approach to separating plants in terms of gene flow is to surround a field with flowers that will attract pollinators of the transgenic crop, so that these trap flowers rather than surrounding wild vegetation would be more likely to receive any transgenic pollen. This approach might conceivably diminish the pollinators' activity in pollinating the crop itself, however. Weed control practices using herbicides or cultivation could also decrease the chance of hybridization between the crop and wild species. A straightforward mechanism is to decrease the length of the boundary of the field and thus decrease the number of opportunities for neighbors along the boundaries to exchange genes. Large, square fields minimize these opportunities (37).

Temporal Barriers

Many problems associated with planned release could be addressed by the timing of the release. For example, if a given engineered line is released in an area with an uncultivated relative that could incorporate the engineered genes, one could manipulate the flowering (phenology) of the engineered organisms so that the crop did not flower at the same time as the weed. For example, wild relatives need short days for flowering, bush type green beans do not (72). Similarly, one could release the introduced plant at a time of year when the weed is dormant or even engineer the crops for cold tolerance, for example, to shift its flowering and production period away from that of its wild relatives. Agricultural experience and ecological understanding will play a significant role in the development of such barriers. Some agronomic practices such as irrigation can allow crop production at a time of year unfavorable for related weeds, diminishing the possibility of cross hybridization.

Crop rotation could be used to force a weed rotation. This could decrease the number of weed individuals present in the field and, therefore, the likelihood of gene transfer; it might also eliminate hybrids produced in preceding crop production periods. Crop rotation could prevent genes from being transferred to weeds outside the field for a whole season or two at a time, diminishing the chances that the gene would become established in the weed community and making it more likely to be lost due to genetic drift. The timing of harvesting could also build a barrier to cross hybridization. For some crops, such as cabbage, spinach, collards, lettuce, sugarbeets, carrots, turnips, radishes, celery, garlic, and onions, the crop product is vegetative; careful harvesting would remove the plants before their flowering, reproductive stage, thereby diminishing pollen transfer (37).

SUMMARY POINTS

Issues and concerns raised by planned introductions of recombinant DNA-modified organisms can be addressed by the integration of risk assessment methodologies with the currently existing knowledge base, continuously augmented by ongoing research and by additional data resulting from field tests. Risk management is therefore possible, with its chief compo-

nents being science-based regulation, scientific management methods, and agronomic management methods. A natural evolution of risk management and regulatory oversight is occurring as our experience base with field tests and in performing ecological risk assessments grows. This step-by-step progression in the use of recombinant DNA-modified organisms in the environment, emphasizing science-based risk assessment strikes a balance between a laissez-faire approach and a paralysis of the use of new technology. Biotechnology has the potential to contribute significantly to agriculture; scientifically sound risk assessment and management promote its acceptance as well as its safety.

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Chapter 9

Issues and Policy Options

Photo credit: MichaelJenkins

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Issues and Policy Options

INTRODUCTION

In many ways, this is an inopportune time for a new technology to appear on the scene. Negative experiences with the nuclear and chemical industries have made the American public wary of new technologies; confidence in institutions has eroded. For both reasons, relative to technologies of the past, biotechnology has been subjected to extensive and apprehensive scrutiny and regulatory oversight. Probably, many institutions will choose to "go the extra mile" to ensure public confidence as some policy issues are resolved. In making policy decisions, it remains important, nonetheless, to distinguish between the technical basis for assessment and regulation of risk resulting from planned introductions of recombinant-DNA modified organisms and what might or might not be done additionally to maintain public confidence. Particular clarity in this regard is called for when assessing possible costs as well as benefits of new biotechnologies. Balancing safety and institutional credibility against economic competitiveness will be a fine art in much demand throughout the decade.

Adequacy of Knowledge Base for Conduct of Risk Assessment

After several years of experience with planned introductions, there seems to be a growing consensus among scientists that the risks of planned introductions of recombinant-DNA modified organisms into the environment can for the most part be assessed with available analytical capabilities.

The fields of community ecology, population biology, population genetics, evolutionary theory, and agricultural science as well as others have contributed to our current understanding of the ecology of planned introductions. Several decades of research in life history dynamics, competition, characteristics of colonizing species or disturbed habitats, disease resistance, and gene flow have provided a basis for risk assessment analysis today.

Of course, further research will add to current knowledge. Many ecologists and evolutionary biologists already are addressing the research questions generated by planned introductions; scientific presentations and publications on this topic are increasing. With increased research funding, more experiments could be undertaken to focus specifically on planned introductions. This may be especially important now as more large-scale introductions are planned. Research is needed in the fields of community ecology, population ecology, population genetics. evolutionary biology, systematic and mathematical modeling, as well as risk assessment methodologies. Interdisciplinary communication among scientists in these fields will be particularly important for future risk assessment of planned introductions.

The relatively young field of risk assessment, which is concerned with the capacity to identify and weigh risks and benefits in a structured and analytical way, has matured rapidly. Experience with other technologically oriented issues, such as pollution control and food safety, has generated principles and methodologies that can be adapted for planned introductions of recombinant-DNA modified organisms in the environment.

The often heard opinion that it is impossible to assess possible risks of any specific planned introduction sets a tone of apprehension over agricultural biotechnology that is belied by this knowledge base. Ecological understanding combined with risk assessment methodologies make it possible to analyze the potential risk of each introduction before it is allowed to take place. However, if American agriculture is to benefit from biotechnology, need exists for public education concerning the extensive capabilities on which scientists draw to ensure the safety of planned introductions of recombinant-DNA modified organisms in the environment.

Adequacy of Knowledge Base for Science- and Risk-Based Regulations

Reports of the National Research Council, the Ecological Society of America, and the scope document of the Office of Science and Technology Policy (OSTP) and Council on Competitiveness all advocate science- and risk-based regulations of biotechnology's applications. The implementation of such regulations draws on the ability of regulators to conduct adequate risk assessments.

Regulations are implemented through oversight by personnel in Federal regulatory agencies, with varying degrees of involvement by State regulatory personnel. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service (USDA-APHIS) has taken the lead in designing a smoothly functioning process for the evaluation of possible risks and benefits when a specific planned introduction is proposed. Technical information to be provided by an applicant is clearly defined, so that

a thorough, science-based risk assessment can be performed. Technical personnel in fields such as genetics and ecology have joined the staff of USDA-APHIS Biotechnology, Biologics, and Environmental Protection Division, to ensure vigorous assessments. State regulatory personnel are drawn into the process so they can provide additional technical information specific to local habitats and add an additional perspective.

The Environmental Protection Agency's (EPA's) Office of Pesticide Programs has extended its review processes under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) to planned introductions of microbial pesticides; it also cooperates with USDA-APHIS in reviewing proposals for introduction of pest-resistant plants. EPA's Office of Toxic Substances recently has published draft regulations to cover planned introductions of genetically modified microorganisms; significant controversy exists as to whether these regulations are indeed science- and risk-based, or whether they simply single biotechnology out for attention because it is biotechnology. The final status of these regulations, and their implementation processes, are not yet known. State agencies have yet to be pulled into EPA regulatory processes to the extent that they are involved in USDA's.

Managing Risks of Large-Scale Introductions

As agricultural biotechnology moves toward commercialization and large-scale planned introductions, the combination of several approaches can maximize benefits and minimize risk. Technically sound implementation processes for science-based regulations are critical to risk management. Technically competent regulatory personnel must work within a framework of adequate technical information to assess actual risks and base regulations on these risks.

Beyond this, specific scientific and agronomic methods are needed to manage risks of particular planned introductions. These might include mechanisms to isolate modified plants spatially, physically, or temporally; to minimize gene flow from modified organisms into natural populations; or to lower the survivability of modified organisms or nontarget organisms that might incorporate a novel gene. The same knowledge base that has led to the generation of recombinant-DNA modified organisms is now being extended toward managing risks presented by them at an extremely fine and precise level of control.

The effectiveness of such methods can be evaluated through monitoring. Various methods of monitoring are being refined to make possible statistically valid sampling for presence or absence of genes or recombinant-DNA modified organisms in other than the target species or the target environment. As monitoring techniques improve, we can extend our knowledge of the basic dynamics of introduced organisms and genes. This will provide a foundation for assessing and managing any risks associated with planned large-scale introductions.

ISSUES

Extent That Regulations Are Product-Based Rather Than Process-Based

The reports of the National Research Council and the Ecological Society of America stated that the techniques of biotechnology are not themselves inherently risky or unmanageable. (See ch. 8.) In line with these findings, the early Coordinated Framework and the scope principles put forth by OSTP and the Council on Competitiveness recommend that biotechnology should not be regulated as a *process. (See* ch. 7.) Rather, a central tenet for biotechnology regulation is that the various *products* of biotechnology should be regulated, just as are products of other technologies. For example, a biotechnology-derived microbial pesticide should be assessed and managed for any risks offered by that particular product in the same way that a traditionally produced microbial pesticide would be handled. Of course, different specific questions may be asked that are appropriate to the techniques and characteristics of each product, but biotechnology is not to be prejudged as especially dangerous.

The product and process distinction has generated a great deal of controversy in the past. However, as the experience base with biotechnology has grown, the premise of judging each product on its own basis rather than automatically implementing special regulations has gained wide acceptance. The extent to which this premise has been implemented is questionable.

USDA-APHIS

Through its focus on plant pests, USDA-APHIS has been able to include, along with other organisms under its purview, any vector, vector agent, donor, organism, recipient organism or any other organism or product produced through genetic engineering if it can be defined as a pest. (See ch. 7.) This approach also makes it possible for regulated articles to become exempted from

special review, as evidence indicates their safety. This provision is particularly important as large-scale commercialization arises.

Even though the oversight net has deliberately been cast broadly in these early days of genetic engineering, the process of genetic engineering itself is not the trigger for special review by USDA-APHIS. Rather, the product or organism itself—and its salient characteristics, such as the vector involved—is the trigger for review primarily in accord with the scope principles.

EPA-FIFRA

Under FIFRA, the Office of Pesticide Programs (OPP) also has applied an existing mandate to products of biotechnology, not only microbial pesticides but also plants that produce compounds aiding them in resisting pests. (See ch. 7.) By pulling these so-called "pesticidal plants" under the rubric of its oversight for pesticides, EPA-OPP seems in one sense to be focusing on the product rather than the process by which it was generated. However, a question exists as to whether or not "pesticides" is the appropriate category for these particular products, especially since naturally occurring and agriculturally bred plants all produce some antiinsect compounds. To assume authority over plants genetically modified to be resistant to pests, EPA-OPP seems to have chosen to look only at plants that had gone through a biotechnology process, leaving naturally occurring and agriculturally bred pest-resistant plants alone.

EPA-TSCA

Under TSCA, EPA's Office of Toxic Substances (OTS) has promulgated a draft rule for oversight of microorganisms that does not fall under other authority. (See ch. 7.) However, under these draft regulations, essentially all microorganisms other than those modified through biotechnology techniques are automatically exempted from review, whereas those modified through biotechnology techniques are labeled "new" and therefore subject to regulation. When the only products subjected to special review are biotechnology products, a question arises as to whether or not the regulations are contradicting the scope principles by focusing on *process.* The draft regulations under TSCA have been charged by some with automatically and unfairly assigning a special riskiness to organisms modified through biotechnology, while exempting organisms known to be potentially dangerous, but that are not produced through a biotechnology process. This discrepancy, and perhaps its final resolution, underscores a central tenet of regulation—that regulation should be based on scientifically determined risk.

Evolution of Regulations

In the early stages of establishing regulation, special attention naturally is focused on the new technology, and a framework of flexible guiding principles is adopted as different agencies begin to deal with its ramifications. Regulations based on scientific assessment of risk begin to be defined. As these regulations are discussed and tested through early implementation, additional scientific data on risk becomes available. Regulators can distinguish between early posited risks and actual risks, as well as identify any risks not predicted in the early days of the technology. As oversight for the products of the new technology becomes more technically valid and precise, based on the salient characteristics of the *product,* it increasingly becomes a matter of standard operating procedure.

As the ramifications of a new technology become more familiar the process behind it subsides in importance and its products provide the focus for risk assessment and oversight. In this way society can benefit from useful new products, while being assured that the risks of that product have been assessed and controlled. With regard to biotechnology, agencies are at various stages of this idealized evolutionary pathway for regulatory oversight. As more experience is gained and data are fed into the system, further progress should be made.

Appropriate Review Authority for Plants Modified Via Recombinant-DNA To Be Pest-Resistant

Under the Coordinated Framework, EPA's Office of Pesticide Programs took on authority for plants into which genes coding for compounds toxic to insects had been introduced. (See ch. 7.) The premise was that these were special ''pesticidal plants' that presented similar risks to the environment, food, and human health as traditional chemical pesticides applied externally in large volumes to plants.

This premise has been questioned for several reasons. EPA-OPP has in the past dealt with chemicals and, to a small but growing extent, microorganisms. For the most part, EPA-OPP has expertise in chemicals and some microorganisms but not plants. Furthermore, compounds that are part of plant tissue obviously do not cause pesticide run-off and other such environmental problems (so long as they are alive); they are distinctly localized. Most of the compounds are not complex, like many synthetic compounds, and may well be more readily biodegradable.

Another key argument with the premise of singling out plants genetically modified for enhanced resistance to pests is that *all* plants have natural pest resistance characteristics. Selection pressures over evolutionary time have favored the spread of genes in natural populations that code for characteristics unattractive or harmful to insects. Furthermore, such characteristics have been selected in breeding programs throughout the history of agriculture. In short, making a distinction between recombinant DNA modified plants and naturally occurring or agriculturally bred plants that are pest resistant is arbitrary, not science-based. If the “pesticidal plant” premise is disallowed, there is then an argument that EPA-OPP is not automatically the best home for regulatory review of such plants. When specific new compounds are introduced into crop plants, food safety testing through FDA, rather than regulations based on the spraying of pesticides, may or may not be more relevant to human safety.

The OPP has not yet finalized the approach that it will take to implement oversight of ‘‘pesticidal plants, ” particularly at a large scale, and USDA-APHIS has been taking the lead at the field trial stage. Companies and universities have moved ahead and conducted tests. Clearly, however, the unclarified status of the OPP's approach to large-scale commercialization worries companies. Moreover, treating all crop plants as pesticides would take an immense toll in State government time and personnel; yet States cannot plan because they have not as yet received guidance from EPA as to what is coming.

Informal suggestions have been made that since USDA-APHIS already takes the lead in field tests of plants genetically modified for enhanced pest resistance, has appropriately trained personnel, and has a clearly articulated approach and established implementation procedures, it could take on oversight authority for large-scale release as well. Whether or not this matches the intent of the original Coordinated Framework, conferring this authority on USDA/APHIS could be compatible with the framework’s product emphasis and would consolidate oversight of plant biotechnology within an efficient, functioning system with a track record of accomplishment in this arena. Perhaps maintaining consultation with EPA personnel would ensure diversity of perspectives on complicated cases.

Delay in EPA Regulatory Development

EPA-Office of Pesticide Programs (OPP)

The OPP’s progress toward implementation of oversight of biotechnology under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) has been patchy. A system has been developed for the oversight of microbial pesticides, whether derived through genetic engineering or not; implementation in this arena is reasonably straightforward. Staff expertise and procedure fairly readily can be adapted to “new” biotechnology. On the other hand, as indicated above, plant expertise is lacking and no clear vision of oversight implementation has been articulated for review of "pesticidal plants," particularly not for large-scale introductions. It is unclear at this time when clarification of oversight might be made; therefore, it is difficult to project a timeframe for regulatory development. It may be that assistance, or perhaps the provision of a model, from another agency could break the logjam.

EPA-OTS (Office of Toxic Substances)

Under the Toxic Substances Control Act (TSCA), new draft regulations have emerged after a prolonged hiatus since the time when earlier draft regulations failed. (See ch. 8.) It is not yet clear whether the new draft regulations will survive. A principal point of controversy is that all microorganisms other than genetically modified ones are eliminated from oversight. Thus, it seems the regulations automatically ascribe special risk to biotechnology processes, contrary to the recommendations by the National Research Council and others. In addition, some proposed regulations subject academic research to the same procedures as industrial research. This has the potential of limiting nonindustrial research done in this area. Clearly defined mechanisms for exempting specific classes of biotechnology-derived microorganisms from TSCA review might soften the impact of the new regulations, but such actions are not evident at this time. By treating biotechnology as an inherently risky process, the regulations send a negative message about biotechnology to the public, as well as to industry and academia, and may well inhibit nonpesticidal uses of genetically modified microorganisms in agriculture and other applications. For example, the emerging industry of bioremediation based on the biodegradation or breakdown of toxic chemicals by microorganisms may be stifled by the TSCA regulations.

Comparison With APHIS Process, Personnel, Structure

EPA’s regulatory logjam might be remedied by adopting the model provided by USDA-APHIS. USDA-APHIS’s track record with field tests has been widely commended. Industry representatives have testified to that effect; en-

vironmentalists appear to have conceded that the system works well at the field trial stage although they remain concerned over large-scale introductions.

Personnel with relevant technical and legal training have implemented USDA oversight authority effectively (see ch. 7), and in a science-based, risk-based manner. The review process is carried out in a straightforward manner. Furthermore. that process and criteria by which applications will be assessed are clearly delineated and accessible to anyone with an interest in how the system works. Experience gained through early field trials is applied to review of later field trials and now is being applied to large-scale introductions. Flexibility, combined with a willingness to learn with experience and change over time, has characterized USDA's mode of operation. The EPA could make good use of all of these regulatory features: use of highly trained personnel with relevant scientific expertise: a clearly delineated and visible process for implementation; and an overall structure with the capacity to evolve over time based on experience gained.

Competitiveness Factor

The delay in EPA regulatory development needs to be addressed because it could impair American competitiveness in the agricultural industry (as well as the environmental industry). Certainly, industry progress should not be facilitated blindly, regardless of risk. Equally important, however, it should not be needlessly blocked in cases where risk is negligible or can be managed. Regulations that are not risk-based send a negative message to industry that can readily stifle innovation. Furthermore, unpredictability itself can have a real impact on corporate strategies; lack of confidence in the eventual settling of the regulatory situation may decrease the uptake of innovative, competitive technologies by American companies.

TSCA Applicability to Living Organisms

Questions arise when a law written for chemicals, specifically TSCA, is stretched to cover living organisms. Essentially, the traditional role of "gap filler" played by TSCA is being extended to planned introductions of microorganisms used for purposes other than as pesticides. (See ch. 7.) Approval for the introduction of microorganisms rests on determination that they will not in some way harm human health or the environment. Microorganisms are not themselves toxic; neither are they likely to be applied in the volumes typical of chemical applications. Instead of persisting as do many synthetic chemical compounds. living organisms are biodegrada ble. However, because they potentially can reproduce themselves and spread in the environment, their use brings up concerns different from those aroused by chemicals.

TSCA could be stretched to cover microorganisms. However, biologically trained staff will have to be given the authority to develop the procedures and requirements of the office. Managers will have to acknowledge the difference between microorganisms and chemicals, and support their biologically trained staff accordingly, when different treatments are necessary. Shifts in regulatory paradigms will have to occur if EPA is to adapt laws, premises, and procedures designed for chemicals to living organisms. EPA's ability to do so appropriately has been questioned.

On the other hand, acceptance of EPA's new regulatory role under TSCA has grown with the passage of time. EPA has yet to prove that it can implement oversight of more than a handful of field trials under TSCA.

A different issue regarding EPA authority under TSCA is that of who is affected. TSCA is a statute explicitly designed to regulate activity conducted "for commercial purposes. Academic research has therefore always been exempt from TSCA oversight. The new draft rules for microorganisms, however, greatly expand the regulatory ''net. Presumably, one rationale (an unusually broad interpretation) for including academic research is that sometimes universities engage in technical transfer or patent filing; or receive research money from companies. Scientifically, the effects of microorganisms placed in the environment by a professor are no different from the effects of those same microorganisms placed in the environment by an industry scientist. However, many question the legal precedent that could be set by extending TSCA's scope to noncommercial research and worry that the draft rules could have a negative impact on academic research. It has been estimated that an application for a single field trial of genetically modified microorganisms could cost between $180,000 and $623,000 (2). Even a cost at the lower end of this scale is more than most universities or research grants will be able to cover, particularly in these difficult economic times. While companies have personnel and budget items dedicated to coping with regulatory processes, universities by and large do not have regulatory policy officials, nor do they even have budget items for the cost of filing applications to regulatory agencies.

Academic research thus could shift away from topics that entail placing organisms in the environment, possibly giving industry a "lock" on this research arena. In spite

of the fact that objective basic research has always played an essential role in this country's development of science and technology. Furthermore, free communication of the results of such research is necessary for the building of a knowledge base to be used in future risk assessments. The absence of academic scientists and their open publication of their research results therefore could represent a significant cost to risk assessment and management.

If under proposed TSCA rules the coverage of academic research is upheld, the agency will need to explore with university representatives a variety of mechanisms for mitigating negative impacts. An alternative application process may need to be developed by the agency, perhaps based on a form already developed that is meant to be streamlined. Other possibilities include giving oversight authority to Institutional Biosafety Committees or to funding agencies, further streamlining the academic's application process, or reimbursing the university for the costs of application.

Implications of Past Treatments of Small-Scale Planned Introductions for the Future of Commercial, Large-Scale Introductions

One key element in successful oversight of large-scale introductions is the effective communication of agency requirements to the applicant. As noted above, USDA-APHIS-BBEP has won kudos from applicants for the clarity of requirements for small-scale field tests. USDA now has drafted a users handbook on how to apply for large-scale introductions. EPA has received more critical reviews, although it has taken steps to outline the information needed from applicants for field testing. It seems likely that the requirements for approval of large-scale introductions will be clarified more quickly for USDA applicants than for applicants to EPA.

Another key element in the development of sound treatment for large-scale introductions is willingness to make use of input from a variety of perspectives. USDA-APHIS has sponsored meetings, among them three (to date) national conferences on Federal and State Regulation of Biotechnology, that are attended by participants from State and Federal Government, industry, universities, and public interest groups. This is one vehicle for ensuring the receipt of outside input. In addition, numerous handouts and other materials make the internal workings of APHIS more visible and, therefore, accessible to outsiders wanting to make comments. EPA personnel also make presentations at conferences, but with the exception of two transgenic plant workshops cosponsored by the agency, they tend to take a less proactive role in fostering a public presence to encourage communication.

Perhaps the key component in facilitating safe large-scale introductions is a clear direction, a set of operating principles, a map with guidelines. USDA preparation of a draft users' handbook for treatment of large-scale introductions is a specific example of a way in which an agency can send clear signals. Certainly, USDA has shown that it is willing to build on its experience with small-scale field tests to begin to come to grips with large-scale introductions in a way that is accessible to applicants. Given its track record, EPA-OPP may be able to move to large-scale introductions of microbial pesticides in a similarly straightforward manner. Whether it can do so for large-scale introductions of plants with enhanced pest resistance properties remains unclear. The recent circulation of draft rules by the Office of Toxic Substances has been a positive step toward clarifying future directions; even as they generate controversy, clarification should eventually be achieved.

With the concerns attendant on any new technology today, it makes particular sense for agencies to monitor the impacts of planned introductions, particularly if potential problems have been identified. Judging by their track records with small-scale field tests, both USDA and EPA seem amenable to appropriate use of monitoring in larger scale introductions.

Effective regulatory treatment of planned introductions is certainly enhanced by competent, technically trained personnel working in a structure designed to facilitate science-based risk assessments, reviews, and decisionmaking. USDA has put together a staff of scientists focused on planned introductions; the structure in which they work has made it possible for the group to learn from experience and to modify the system so that relatively unfamiliar or risky applications can receive the most attention. EPA's OPP can draw on microbiologically trained personnel, but does not have the plant specialist staff of USDA. EPA's OTS has had so few biotechnology applications, all but one of which were from the same company, that it is hard to extrapolate as to the effectiveness of personnel or structure for future cases.

Clearly, sound, effective oversight of large-scale planned introductions will make a difference to the future of agricultural biotechnology and thus to the future of agriculture. (See ch. 7.) Review processes that protect human health and the environment while still facilitating safe introductions will benefit the competitiveness of American agriculture by ensuring the uptake of new techno-

logical tools. The American economy will be harmed, on the other hand, by unnecessary blocking of these new technological tools through:

- reviews based on criteria that are not science or risk-based;
- unclear directions within regulatory agencies;
- inadequate communication of requirements;
- minimal learning from experience and from input from outside perspectives; or
- insufficiently trained personnel in a structure not conducive to building on experience and streamlining procedures while maintaining safety.

As the era of large-scale introductions opens, the challenge before EPA as well as USDA is to strike the appropriate balance of protecting the American public's health and environment while allowing the American public to benefit from significant advances in agriculture.

States and the Federal Regulatory Process

The USDA has an extensive network of partner State organizations throughout the country, and has been able to bring appropriate State government officials into the review process for planned introductions (ch. 7). In addition to identifying appropriate contacts and sending them copies of applications for that State, USDA has integrated the State-level review into its own review "timeline. " State officials are respected for the germane local issues and environmental knowledge they can contribute. In addition, USDA has underscored its partnership relationship with the States by holding three annual national Conferences on Federal and State Regulation of Biotechnology at which information and views were shared, communication improved, and issues raised. USDA can be regarded as a model for the inclusion of States as partners in oversight of planned introductions.

EPA under FIFRA has somewhat of an analogous relationship to the States, in that State officials implement Federal rulings regarding monitoring, labeling, and other treatment of pesticides. The lack of clarity in OPP as to future handling of plants genetically modified for enhanced pest resistance, however, has significant ramifications for the States. State officials charged with implementing FIFRA and setting up the procedures for handling "pesticidal plants" have complained of being in the dark about EPA policy with regard to these products. Mechanisms to improve communication between the Federal officials setting policy and the state personnel who will have to implement it are needed as soon as possible. (See ch. 7.)

Federal officials under TSCA barely have initiated relationships with State agencies. and there is no explicit legal directive for TSCA to involve State officials. There is no tradition of connection between specific State environmental department personnel and the Office of Toxic Substances, yet States are interested in being involved in biotechnology-related policy and implementation. A joint biotechnology meeting for State and EPA regional personnel, to explore ramifications of the draft TSCA rules, would be a positive step toward building relationships with the States.

Potential Conflict of Interest Within USDA

USDA occasionally has been accused of conflict of interest in that it both funds research to promote agriculture and regulates agriculture. (See ch. 7.) USDA officials point out that the Department of Health & Human Resources also has within it both the research-funding National Institutes of Health and the regulatory Food and Drug Authority. More specifically, however, USDA-APHIS-BBEP has several important "checks" built into the system that greatly decrease the chances for conflict of interest. One significant check is provided by the openness of the system; the workings of BBEP are highly visible. Information is readily accessible through presentations, widely available printed materials, and responses to inquiries.

Another check is provided by the inclusion of States in the permit process. State officials watching out for the well-being of their own State provide external yet informed monitoring of APHIS decisions. In addition to being monitored continually by State officials, the APHIS system is sufficiently open that specters of conflict of interest can in all probability be laid to rest.

Risks of Genetically Modified Plants or Microorganisms Becoming Pests

Any novel organism potentially represents some level of risk to the environment, whether that organism is naturally occurring or genetically modified. Therefore, for any new variety, some risk assessment is appropriate.

The likelihood of a genetically modified plant or microorganism actually becoming a pest, however, is relatively low. (See ch. 8.) The track record of agriculture (in a sense, a form of long-term genetic engineering) has shown that current crops are not likely to become established as weeds. For the most part, long-established mechanisms for containment in agricultural systems have been highly successful in the United States. Moreover,

recombinant-DNA modified organisms, unlike wild, naturally occurring organisms, are *designed* to exist only in a specific environmental regime—the nurturing surroundings of a cultivated field.

Microorganisms modified for agricultural purposes are constrained somewhat similarly to plants, although they probably are not so dependent on cultivation for continued survival. However, the extensive agricultural experience with microorganisms (i.e., microbial pesticides) has not resulted in a pest problem. To become a pest organism, an agricultural plant or microorganism has to exist independently of cultivation—outside the planted field. Several steps are necessary to its success; each one, from dispersal to the production of viable, competitive offspring, is relatively unlikely to occur. (See ch. 8.) In general, the chances of a genetically engineered plant or microorganism becoming established as a pest are low, simply because each step of the process is fraught with difficulty.

Gene Transfer or Cross-Hybridization Between Genetically Modified Plants and Wild Plants

Cross-hybridization, the crossing of two plants of different species to produce fertile offspring, is a rare phenomenon. (See ch. 8.) While gene transfer between individuals of the same species is, of course, straightforward, gene transfer between different species is not; their genomes, or genetic compositions, are usually sufficiently different that they do not line up and match well for the key molecular and cellular events of reproduction, Even if a transferred gene were involved in such a cross, it would be cast onto an ‘‘alien’ genetic background—its expression could be problematic. Even if a viable first generation resulted from such a random crossing, as in the case of a horse crossed with a donkey producing a mule, that hybrid would most likely be sterile, so the new recombinant gene would not be passed along.

In any case, most crop species in the United States do not have indigenous weedy relatives with which they could cross-hybridize. Canola is the only major crop for which there are related weedy species in the United States. A recent conference on large-scale introduction of canola analyzed the ramifications of the potential for cross-hybridization and made recommendations for scientific and agronomic risk management. (See ch. 8.)

The possibility of cross-hybridization is greater in other countries, where crop species and related weedy species do coexist. Weedy species of rice, for example, can impose tremendous economic costs in the far East. Canola has many relatives in Europe. The developing countries, in particular, are the center of origin for many crop species. This means that related weedy species are especially likely to be found close to agricultural fields. Stocks of an ancestral line could conceivably be “contaminated” through cross- hybridization with any crop plant, including genetically modified plants.

As it exports agricultural biotechnology capabilities, the United States should offer advice to developing countries as to the management of risk from cross-hybridization. Agency regulatory staff have already begun this sort of communication, passing on information regarding scientific and agronomic mechanisms of risk management and encouraging their regulatory colleagues to employ such mechanisms. This advisory function needs to grow with the export of technology; also, companies, foundations, and international agencies need to integrate risk management transfer with their agricultural biotechnology technology transfer to developing countries.

Regulations on a Case-by-Case Versus a Generic Basis

Currently, review of applications for field trials is done on a case-by-case basis. This approach has been recommended for several reasons. (See ch. 8.) First, we are learning by doing as we handle a new technology, so one step at a time has seemed appropriate. Specifically, each field test is unique in terms of the transferred gene, the vector by which that gene is transferred, the recipient individual’s genetic background, the resulting combination of phenotypic characteristics, the likelihood of further gene flow, and the likely impact of the phenotypic characteristics on various components of particular target and nontarget environments. Risk assessment should focus on those unique aspects of a field trial that may present potential risks.

A rationale also exists for reviewing applications by grouping them into generic categories for which guidelines of “approvability” have been developed. Risk assessment review would certainly be more streamlined under this approach. As knowledge is gained, categories can be updated continually.

Key reports have stressed “familiarity” as an appropriate theme for risk assessment: if we are familiar with a component of an application package (a particular organism, or vector, or characteristic, for instance) we more readily can assess the level of risk it presents than if it is new. As we become more familiar with greater numbers of genetically engineered products (through research and field trials) it should become easier to predict

the levels of risk they present and to design effective management. Thus, as oversight for planned introductions of recombinant-DNA modified organisms into the environment naturally evolves, certain (more familiar) categories of features automatically may be designated low risk, or high risk depending on certain conditions. However, each feature might be double checked for any specific idiosyncratic risk it might present; the overall package of features also might be assessed to ensure that no interactive effect among the features produces a new level of risk. The recipient organisms and vectors, may be the first features of biotechnology introductions to be categorized by riskiness; the characteristics most likely to be transferred eventually might be broadly categorized. The interactions between the genetically modified organism and the local environment (including probability of gene flow) will always bear close scrutiny, even if general categories suggest just what needs to be examined to assess risk.

The evolution from case-by-case to generic categories as a basis for review is likely to occur naturally; it is dependent on the accumulation and analysis of knowledge gained in the early stages of dealing with a new technology. Risk assessment of planned introductions of recombinant-DNA modified organisms now is undergoing this evolutionary process.

POLICY OPTIONS

ISSUE: The tools of biotechnology offer great potential to American agriculture; regulatory treatment of any agricultural products derived with such tools will play a dominant role in any related gains or losses in economic competitiveness. Science- and risk-based regulation of products can ensure safety without unnecessarily impeding the economy.

Option: Congress could direct Federal regulatory agencies to make science-based, risk-based regulation of biotechnology products (not process) a unifying policy across agencies.

This would be a clear message to the executive branch that Congress expects a unified approach across Federal agencies based on the product not on the process. Communication through interagency groups would help to ensure a common approach based on scientifically determined product risk. This approach can help protect health and environment and, at the same time, should generate a comprehensible, workable regulatory apparatus for incorporating the tools of biotechnology into American agriculture. However, EPA will need to address staff needs to conduct technical risk-based reviews.

Option: Congress could direct appropriate agencies to review and regulate biotechnology as a process, rather than the products.

EPA-OTS has been accused of regulating the process of biotechnology, not the products, in its proposed rules, for example. It would be a clear signal that biotechnology is so unique that it must be scrutinized for each use. This would satisfy those concerned with the application of biotechnology to agricultural products. However, no scientific evidence exists to justify such an approach. If some agencies ignore the use of risk assessment of products and automatically penalize any efforts made using biotechnology, several impacts are likely to occur. Industries and universities would be likely to "agency-shop, ' orienting their efforts toward the agency with the clearest analytical assessment of science-based risks—that agency will be the least arbitrary and the most predictable, an approach certainly favored by industry. Research and industry activity in areas not regulated on the basis of science-based risk would diminish, at what may be a real cost to society. The agency regulating biotechnology as a process sends out an obvious negative message to industry and perhaps an equally important, if more subtle, message to the public. Regulations based on the assumption that biotechnology is inherently unpredictable and highly risky can lead to public reaction and political pressures that may be detrimental to the economic competitiveness of American agriculture.

ISSUE: Enhanced pest resistance is one of the most promising applications of the tools of the new biotechnology. Obstacles to its development could send a negative message to agribusiness, slowing its incorporation of biotechnology as a mechanism towards increased economic competitiveness.

Option: Congress could keep the oversight authority for plants genetically modified for enhanced pest resistance under EPA Office of Pesticide Programs (OPP), but direct EPA to strengthen OPP.

If oversight of “pesticidal plants” introduced at a large-scale is to be handled by OPP, several implementation steps would need to occur. Technical staff with plant expertise would need to augment current staff; clear definitions would have to be devised for review, given that some naturally occurring plants contain more ‘‘pesticidal compounds” than will the products of biotechnology;

communication with State-level implementors would need to be improved immediately; and a clear approach (even if wisely flexible over time) would have to be articulated, so that the public, industry, and academia would know where the agency stands and how it will implement its policy.

Option: Congress could direct USDA-APHIS to regulate large-scale introductions of plants genetically modified for enhanced pest resistance.

Since USDA-APHIS-BBEP has taken the lead for field tests of plants genetically modified for enhanced pest resistance, APHIS could handle large-scale introductions. This has the advantages of centralizing plant oversight and making effective use of an already well functioning technical staff and organizational unit. The chief disadvantage would be a departure from the Coordinated Framework, which ascribed authority to EPA-OPP.

Option: Congress could direct EPA to work with USDA to develop a similar model of operation and to report on progress to Congress within a specified period of time (e.g., 6 months).

Despite disadvantages of 'forcing' two very different offices to work closely together, this has the advantage of allowing USDA to handle any risk concerns related to planned introductions, while allowing EPA to continue to handle food safety concerns related to "pesticidal" toxins in the food supply. USDA has established a strong track record for taking the lead in field tests of pest-resistant plants; it is on the verge of establishing a track record in handling large-scale introductions generally. Building on this base such that USDA handles large-scale introductions of pest-resistant plants is a logical extension of capability and responsibility. Similarly, EPA has developed expertise in setting tolerance levels for pesticides in plants; after scientifically determining the relative risks of genetically engineered pest-resistant compounds compared to naturally occurring compounds, it could set tolerances in this case as well.

ISSUE: TSCA is a statute explicitly designed to regulate activity "for commercial purposes.>' Academic research, therefore, has been exempt from TSCA oversight. The proposed draft rules for microorganisms, however, greatly expand the regulatory "net." One rationale for including academic research is that sometimes universities engage in technical transfer or patent filing, or receive research funds from companies. Obviously, the effects of microorganisms being placed in the environment by a university scientist are no different from the effects of those same microorganisms being placed in the environment by an industry scientist. Concern exists, however, that the draft rules could have a negative impact on academic research.

Option: Congress could allow the proposed rule to stand, placing the same requirements on academic research as on industrial research.

Subjecting universities to the requirements placed on companies seems contrary to Congressional intent behind TSCA. It could have significant impacts on university research. Faced with the added bureaucracy and high costs entailed by this rule, the majority of university researchers might deliberately avoid planned introductions of genetically modified organisms. This would leave industry in charge of an area of research that could continue to benefit from objective, openly published study. Such a situation would inhibit the production of new knowledge for use in future risk assessments. However, it is an arbitrary decision to automatically exclude universities from oversight—the release of organisms that pose a risk should be regulated regardless of who conducts the release.

Option: Congress could direct EPA to develop an oversight mechanism by public scientists for planned introductions as an alternative to the proposed TSCA rule.

Universities could make use of their already existing system of oversight committees and institutional biosafety officers to regulate biotechnology field trials "in house. " Just as the Institutional Biosafety Committees (IBCs) review laboratory research involving recombinant DNA, they could review proposals for planned introductions (3). It would entail education of laboratory-oriented personnel as to the ecological considerations of field release, as well as possible expansion of committee membership to include appropriate disciplines. Serving on an IBC is a time-consuming effort for university personnel. Many feel that there are already too many university committees on which they must serve and that there time could be used more productively. Use of those committees to provide oversight is a possible trade off for the university between being able to conduct this research or not.

Option: Congress could direct EPA-OTS to develop special procedures to minimize or eliminate the

regulatory burden on universities, to ensure that public research continues in this area, and to report to Congress on the method selected and its results.

This option would still hold public scientists accountable but would be aimed at lessening the regulatory burden if the appropriate procedure is used. Several possible procedures exist. One possibility would be that the agency funding the research would take the responsibility for monitoring and reviewing the work. As part of the funding contract, the principal investigator agrees to follow EPA guidelines on management and to contact EPA if the need arises. This makes it possible for the funding agency to monitor the project and enforce regulations through the distribution of funds (1).

Another approach is to streamline the application for public researchers. For example, an abstract from a grant proposal would be sufficient to trigger important questions that arise about the project from EPA. Another possibility would be for EPA to set aside a budget that would reimburse universities for costs incurred in filing an application. However, even if a cost-savings mechanism is developed. a bureaucracy-minimizing mechanism will also be necessary if Congress desires to encourage public researchers and their home institutions to conduct the objective research that will contribute further to our knowledge base.

Option: Congress could amend TSCA to exclude universities or to provide alternative means to regulate academic research.

An argument can be made for including academic researchers. Obviously, genetically modified organisms released into the environment by a public researcher have the same effect as the same organism placed into the environment by an industry scientist. On the other hand, concern exists about the legal precedent that could be set by extending TSCA's scope to noncommercial research and that it could have a negative impact on research. An application fee for a single field trial costs between $180,000 and $600.000. Even the lower cost is more than most universities or research grants are able to cover. Even though companies have personnel and a budget to cope with regulatory processes. universities for the most part do not have regulatory policy offices or the budget for filing applications. Congress could make its intent for universities clear by stating it in legislative language through TSCA.

ISSUE: As large-scale planned introductions become imminent, companies are looking to the regulatory agencies for guidance as to how to proceed. Clear guidance is critical to commercial development of agricultural biotechnology.

Option: **Congress could** direct *EPA-OPP and OTS to clarify their regulatory approaches to large-scale introductions and report back to Congress within a specified period of time.*

The interagency work groups. as well as leadership of EPA, can orient efforts toward assisting EPA staff in clarifying the regulatory guidelines. A flexible approach, capable of evolution as additional data are gathered seems appropriate, and individual case discussions between EPA and applicants are useful. Clarifying regulatory guidelines would be particularly helpful to agribusiness working with "pesticidal plants" or microorganisms other than microbial pesticides. USDA-APHIS-BBEP could provide model mechanisms for clear communication of requirements, use of input from outside the agency, addition of technologically trained personnel, and creation of an effective structure as well as clarification of direction.

Option: Congress could direct EPA to continue on its present course.

This is basically a status quo option. It would mean a continuation of the lack of clarity of regulating policy for potential applicants at the large-scale stage. The absence of applications to EPA-OTS for environmental release under TSCA over the last year may illustrate industries' response to lack of predictability in the regulatory arena. It also undermines public confidence in the ability of regulatory agencies to regulate biotechnology.

Option: Congress could conduct oversight hearings of EPA and USDA reguarding regulatory policy for large-scale release.

Oversight hearings could assist the agencies in developing policy to meet congressional intent for regulating these products even though the regulatory agencies have stated that current laws are sufficient for regulation of products derived from biotechnology. This could help clarify differences in laws written primarily for chemicals instead of genetically modified organisms.

ISSUE: The institutions handling new technology, including biotechnology, need credibility. In the past, far less attention was paid to this issue; today several elements of what should be "standard operating procedure" can be emphasized by institutions to gain or maintain vital public trust. A balance between maintaining public interest and ensuring industry competitiveness must be achieved.

Option: Congress could direct EPA and USDA to emphasize: 1) increased input of public participation into their systems; 2) an open process; 3) scientifically sound procedures communicated clearly to other scientists; and 4) follow-up on appropriate cases.

Most systems are sounder when external input is factored into decisions. External advisory committees, hearings, and informal workshops are examples of mechanisms by which Federal agencies can obtain such input. EPA-OPP, for example, cosponsored workshops on transgenic plants to gain scientific advice as they deliberated on their approach to so-called "pesticidal plants, " and has used its scientific advisory board in deliberations over the draft TSCA rule. USDA-APHIS has held a variety of conferences and workshops, stressing public input and State officials' input. In fact, USDA-APHIS has made State input an integral part of its review process; EPA could wisely adopt this approach, in OPP and OTS. Input at the State level can provide important relevant ecological information, perhaps equally important, it serves as a credible system of external checks and balances on a Federal agency.

By developing scientifically sound procedures for data needs and communicating them clearly, an agency can build an accessible database and contribute to and benefit from the scientific community. USDA's Agricultural Research Service is complementing the work of APHIS by building a database on field tests. The draft TSCA rule refers to a similar accumulation of data, although specific implementation processes could be made clearer. Along with ARS, USDA-APHIS-BBEP, in particular, has highly trained staff in relevant areas to interact with outside scientists.

Parties concerned about a new technology want to know that potentially problematic cases are being subjected to followup. While USDA and EPA can and do impose monitoring requirements on field tests, both agencies could benefit from selectively implementing more extensive followup (perhaps by monitoring indicators identified for a possible worst-case scenario) on specific cases that might prove troublesome. This is, of course, time consuming. This approach should be used in a manner that does not put undue burdens on straightforward cases; but so that the public feels secure in the knowledge that problematic cases will be tracked past the time of introduction.

Option: Congress could require regulatory agencies to develop explicit plans for building public confidence and report those plans to Congress.

This option would give agencies maximum flexibility. It would allow for the evolution of regulation based on the experience of the agency. Moreover, this approach would allow for a true solution to be developed within the agency as opposed to it being imposed on the agency from outside. Reporting the plan to Congress would allow the public to express its opinion and to exert pressure on the agency to change those parts of the plan found to be to unacceptable. On the other hand, it is a time consuming effort for the agencies and Congress. With the large demands on Congress, some members could be concerned that it was not the best use of their time.

Option: If regulatory agencies fail to maintain public confidence, new law(s) or congressional oversight could be established to satisfy the public demand for accountability.

This option is relatively drastic and could have several disadvantages. Managing a system from the outside invites logistical and other difficulties. Moreover, the tendency with this approach would be to "freeze" procedures at a particular moment. This could hamstring the natural and positive evolution of regulation, such as the gradual extraction of generic principles from case-by-case reviews. More generally, this approach would be more in the nature of imposed management rather than a true solution developed within the agencies; as such its own credibility may be weakened. However, it is an option that could ensure accountability to the public if regulatory agencies are incapable of doing so themselves.

CHAPTER 9 REFERENCES

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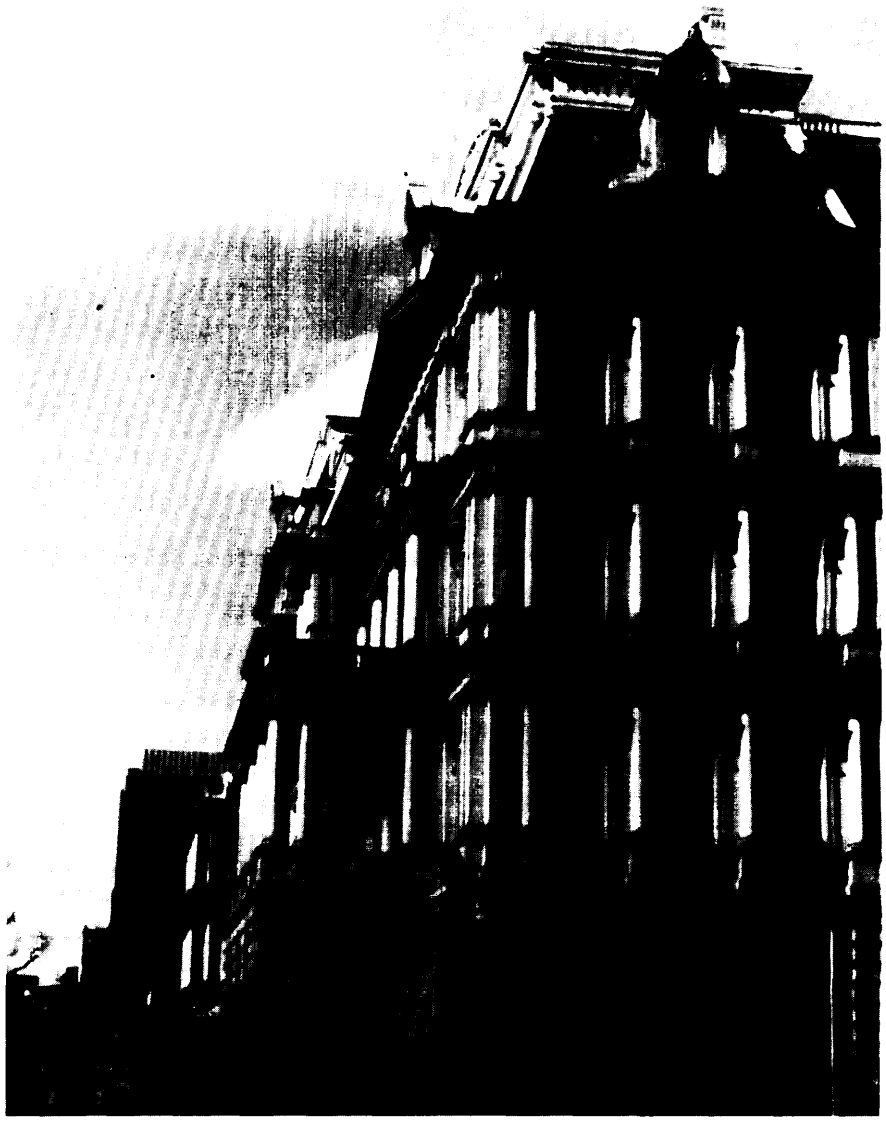
Part IV

Food Safety and Quality

Chapter 10

Regulatory Agencies and Their Statutory Authority



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Regulatory Agencies and Their Statutory Authority

In the United States, five Federal agencies operating under a variety of laws have primary responsibility for maintaining the safety of the food supply (box IO-A). These are the Food and Drug Administration (FDA); the U.S. Department of Agriculture (USDA Food Safety and inspection Service; USDA Agricultural Marketing Service); the Environmental Protection Agency (EPA); and the National Marine Fisheries Service (NMFS).

THE FOOD AND DRUG ADMINISTRATION

The Food and Drug Administration, within the Department of Health and Human Services, is responsible for ensuring that domestic and imported food products sold in interstate commerce are safe, sanitary, nutritious, wholesome, and honestly labeled. For the purpose of oversight, food is defined as 1) articles used for food or drink for man or other animals, 2) chewing gum, and 3) articles used for components of any such article (U.S. Code, 1982a, Title 21, Food and Drugs, sec. 321(f)). By this definition, food includes that consumed by human beings as well as by livestock. Because animal drugs may leave residues in meat consumed by humans, FDA also has regulatory authority for drugs used in livestock.

FDA's Center for Food Safety and Applied Nutrition (CFSAN) is responsible for conducting and supporting human food safety research; developing and overseeing the enforcement of food safety, quality, and labeling requirements of the Food, Drug, and Cosmetic Act (FDCA); coordinating and evaluating FDA and Federal/State cooperative surveillance and compliance programs relating to foods; and developing and disseminating food safety and regulatory information to consumers and industry. FDA's Center for Veterinary Medicine (CVM) regulates animal drugs and livestock feeds marketed in interstate commerce, and is responsible for the safety of these veterinary products.

Statutory Authority for FDA Regulation of Food Products

The first food safety law passed in the United States was the Food and Drugs Act of 1906. This law contained provisions for the seizure of adulterated foods, that is, foods that contained added poisonous substances or other added substances that were deleterious and that may render the food injurious to health. In 1938, this act was substantially revised to become the Federal Food, Drug, and Cosmetic Act (FDCA), which still authorizes FDA's food safety responsibilities.

Like the Food and Drug Act, the FDCA authorizes control of adulterated foods caused by added substances, and extends the adulteration clause to cover naturally occurring substances (Section 402 (a) (1)). FDA takes a

Box I0-A–Federal Agencies Primarily Responsible for Food Safety

Agency	*Principal statutory authority*	*Responsibilities*
Food and Drug Administration	Federal Food, Drug, and Cosmetic Act	Safety/quality/effectiveness of animal feeds and drugs, and all foods except meat and poultry.
USDA-Food Safety and inspection Service	Federal Meat Inspection Act and the Federal Poultry Products inspection Act	Safety/wholesomess/accurate labeling of meat and poultry products
USDA-Agricultural Marketing Service	Egg Products Inspection Act	Safety/quality of egg products and shell eggs.
Environmental Protection Agency	Federal Insecticide, Fungicide, Rodenticide Act	Safety of Pesticide products
	Federal Food, Drug, and Cosmetic Act	Pesticide residue tolerance in food feeds.
National Marine Fisheries Service (also FDA, PHS)	Agricultural Marketing Act	Voluntary Seafood Inspection

SOURCE: Office of Technology Assessment, 1992.

broad view of what is considered added, and this view has been upheld in several court cases. Any substance that is not an inherent natural component of food may be treated as an added substance, including but not limited to, those of environmental or industrial origin that become components of food (e.g., mercury in fish). Consequently, pollutants from the air, pesticide residues, and minerals from fertilizers, for example, all fall within the scope of added substances (9).

The distinction between an added substance and a natural substance is substantial because added substances are held to a higher safety standard. The FDA can request that legal action be taken against inherent natural components of food if that substance *would ordinarily* render the food injurious to health. For added substances, if the FDA can establish that a substance *may* render the **food injurious to health,** the food is adulterated under FDCA. Under this standard, FDA must show only that there is a reasonable possibility that the food will be harmful if consumed. The FDA rarely applies the standards for natural components except for obvious cases such as crops that produce cyanide when improperly processed (e.g., cassava, lima beans, etc.). Other sections of the FDCA (406 for example) authorize FDA to establish tolerances for added substances when their presence in food cannot be avoided or if their use is necessary to produce the food (9).

The FDA is responsible for demonstrating that a food is adulterated. As originally enacted, the FDCA provided no authorization for the premarket evaluation of added substances. FDA could only challenge a food ingredient after it was marketed. However, rising concern over the addition of chemical additives to foods prompted Congress to enact the Food Additives Amendment in 1958. This FDCA amendment broadens the definition of adulterated foods to include those foods that contain any food additive not specifically approved by the FDA (Section 402(a)(2)(c)). Approval is granted in the form of a regulation, which shifts the burden of proof for the safety of these additives to the food industry (7, 8, 9). This amendment defines a food additive as:

> A **substance, the intended use of which results or may reasonably be expected to result, directly or indirectly in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or,** in the case of a substance used **in food prior to January 1. 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use. [U.S. Code 1982c, Title 21, Food and Drugs, Sec. 321(s).]**

The FDCA also covers the regulation of pesticides, color additives[1], and new animal drugs. Additionally, substances used in accordance with a sanction of approval granted prior to September 6, 1958 under FDCA, the Federal Poultry Products Inspection Act and/or the Federal Meat Inspection Act (i. e., the prior sanctioned substances) are not included in the definition.

To avoid placing unnecessary restrictions on the development of new food additives or forcing the evaluation of food additives already safely used, Congress provided for some exceptions to the food additive amendment. One clause, for example, allowed the continued use of a substance that is generally recognized as safe (GRAS) by qualified experts for its proposed use in food (U.S. Code 1982c, Title 21, Food and Drugs, Sec.321 (s)) (9).

GRAS food ingredients are those generally considered safe by qualified experts based on either 1) a safe history of use in food prior to 1958 or 2) scientific information (U.S. Code 1982c, Title 21, Food and Drugs, Sec.321(s)). A safe history of use generally involves substances of natural biological origin widely consumed for their nutrient properties prior to January 1, 1958, are subject only to conventional processing as practiced prior to 1958, and exhibit no known safety hazard (FDA 1986b, Title 21, Food and Drugs, Sec.346), To be granted GRAS status based on scientific information requires expert knowledge backed by "substantial support in the scientific literature' (Weinberger v Bentex Pharmaceuticals 1973, U.S. Reports 412,645) (9).

The same quantity and quality of scientific evidence is required to obtain regulatory approval of a food additive or a GRAS substance. The information critical to affirming a substance as GRAS must be widely available and generally published. The validity of the published literature must also be agreed to by those qualified to judge food safety issues. Disputes by qualified experts

[1] Col$_{or}$ **additives are materials that are dyes, pigments, or other substances** chemically synthesized **or extracted, isolated, or otherwise derived** with or without change from vegetable, animal, mineral, **or other sources** that **are capable of** imparting color (including black, white, and gray) to food, drugs, cosmetics, or the human body. Color additives must receive **premarket** approval or be GRAS.

could prevent the granting of GRAS status. Thus, obtaining affirmation of GRAS status can be more difficult than obtaining regulatory approval as a food additive (21 CFR 170.30).

The FDCA requires premarket approval only of food and color additives. By a strict interpretation of the food additive amendment, any substance that becomes a component of food, or affects the characteristics of food, may be regulated a food additive. This implies that the development of new crop varieties could be classified as food additives. FDA has rarely enforced this strict interpretation, however. New crop varieties have generally been viewed as not being so significantly different from crops consumed prior to 1958 to warrant formal review of the GRAS status. However, FDA can review the GRAS status of substances of natural biological origin that have undergone significant changes as a result of breeding and selection or a new process introduced into commercial use after 1958 (FDA 1986c, Code of Federal Regulations, Title 2 1,Food and Drugs, Sec. 170.30(f))(9). A *significant* increase in the use of a particular food ingredient, a change in the composition of the food ingredient, or a change in the manufacturing method could trigger a loss of the GRAS status based on the common use in food criteria. Substances altered such that they are no longer generally recognized as safe are regulated as food additives (9, 14). FDA can review food products derived from a new variety of food crop prior to marketing if that crop is known to contain toxins that have the potential to be acutely toxic if in high enough concentration.

In addition to the authority to regulate adulterated foods, FDCA also confers on FDA authority to remove misbranded foods from the market. Food products are considered misbranded if, among other things:

. the labels are false or misleading,
. if they are offered for sale under the name of another food,
. if they are an imitation of another food and the label does not clearly state so,
. if the container fill is misleading, and
. if label information required by law is not present.

Statutory Authority for FDA Regulation of Animal Feeds and Drugs

The Center for Veterinary Medicine (CVM) carries out FDA's Animal Drugs and Feeds Program. CVM is responsible for ensuring that drugs administered to, and feeds eaten by, animals are safe and effective for the animal, are properly labeled, and produce no human health hazards when used in food-producing animals. For the purpose of regulation, an animal drug is defined in part as ''articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in animals' (21 U.S.C. section 321(g)). Animal feeds are considered to be articles used as food for animals or intended to provide a substantial source of nutrients for animals (21 U.S.C. section 321(x)). CVM is responsible for monitoring animal drug sales and distribution as well as good manufacturing practices (i. e., compounding, formulation, and production and manufacturing) associated with animal drugs and medicated feed production. FDA estimates that about 80 percent of the livestock and poultry in the United States is treated with some animal drug or medicated feed. FDA's automated animal drug data system contains information on over 12,000 animal drug products (18).

The FDCA provides the statutory authority for FDA regulation of animal feeds and veterinary drugs, and its provisions are the same as those for human foods: Thus, FDA must provide premarket approval for new animal drugs and for new additives (e.g., medications) that may be included in livestock feed; pesticide tolerance levels are set by EPA for livestock feeds, as they are for human foods; pesticide and drug residue levels are established for meat products that might be consumed by humans.

GRAS status can also be granted for livestock feed additives. Similar to human food additives, livestock feed additives can attain GRAS status if they have a substantial history of safe consumption by a significant number of animals in the United States or by scientific consensus. Adulterated or misbranded products can be removed from the market using the same criteria that apply to human foods (21 CFR 570.3 (f)).

Outside Input Into the FDA Decision Process

The FDA uses notice and comment procedures for decisions concerning food additives and advisory committees for decisions concerning human drugs. Any person may petition FDA to establish a food additive regulation to approve the use of a food additive (21 U.S.C. 409(b)(l)). If a regulation is required, a notice of that decision is published in the Federal Register. Following publication of a final rule, any person who might be adversely affected by the proposed decision has 30 days to request a hearing. FDA is not required to publish receipt of a new animal drug application.

Public participation in new drug approvals comes primarily from the use of advisory committees. FDA currently has 38 standing advisory committees of which almost all are concerned with human drugs and medical devices. There is one veterinary drug advisory committee. FDA uses advisory committees to provide expert opinion, and as such the voting members of the committees are usually technical experts. Some committees have nonvoting industry and public representatives. FDA generally does not use advisory committees for food additive petitions, but does seek input from scientific organizations such as the National Academy of Science and the Federation of American Societies for Experimental Biology (2, 10, 16).

FDA Inspection Activities

All FDA inspection and enforcement activities are carried out by the Office of Regulatory Affairs (ORA). The ORA is headquartered in Rockville, MD and has field offices in 49 States and Puerto Rico. Six regional offices coordinate the activities of all of the various FDA offices and coordinate FDA activities with those of State authorities. Facilities to test products for safety, quality, and conformance with labels are provided by 21 district offices and 18 district laboratories. The Office of Regulatory affairs also conducts research necessary to evaluate health hazards and to develop detection methodologies. Additionally, there are 136 resident posts staffed with inspection personnel (18).

FDA considers its food safety responsibilities as being primarily preventive rather than corrective. Its resources are inadequate to continuously monitor every sector of the food industry (table 10- 1). Therefore, FDA tries to ensure that safety is "built into" products rather than to continuously monitor for safety after the products are produced. However, FDA's ability to carry out its responsibilities is being strained by the lack of resources. While the workload increased during the 1980s, FDA had nearly 8 percent fewer staff and 8 percent less funding in 1989 than in 1980 (17).

FDA's food inspection procedures focus primarily on inspecting food establishments for sanitation, ingredient labeling, nutrition labeling, good manufacturing practices. low-acid canned foods, acidified foods, and food standards, although follow-up monitoring of some marketed food products is conducted (primarily for microbial contamination and chemical residues).

The number of food establishments in the United States is enormous-at least 636,000 in 1991. About 53,000 are subject to FDA inspection in that they produce products sold in interstate commerce or products made in whole or in part from ingredients shipped in interstate commerce. The States regulate firms that produce **food** products that contain no ingredients shipped in interstate commerce and are to be sold only within that State. The States also have primary inspection responsibility in some food and drug areas such as **milk, shellfish, retail food stores,** and food service establishments (restaurants). To help carry out its regulatory responsibilities, FDA cooperates with State agencies to cover all food establishments.

FDA can contract State programs to inspect firms within its responsibility. In fiscal year 1989, FDA had 113 contracts in 45 States and Puerto Rico at a cost of approximately $5.3 million. FDA and contracted State agencies inspected nearly 17,000 food establishments and analyzed over 20,000 laboratory samples in 1991 (table 10-2) (18).

For those food establishments under direct control by State agencies, FDA has established cooperative agreements. These agreements are valued at approximately $175 million, involve over 400 different State agencies, and cover millions of sites where **food is sold or processed (table 10-3) (18).**

Table 10-1—FDA Staffing Levels, Selected **Years**

Staffing	1980'	1985[a]	1988[a]	1989[a]	1990	1991	1992
CFSAN	976	859	826	817	821[b]	884[b]	895[b]
CVM	238	253	244	244	278'	282[c]	284[c]
ORA							
Headquarters	94	106	112	114	NA	NA	NA
Field offices	1,222	1,118	1,151	1,162	**NA**	NA	**NA**

NOTE: Not all of CFSAN and CVM personnel are directly involved in food safety and quality activities.

KEY: CFSAN = Center for Food Safety and Applied Nutrition; CVM = Center for Veterinary Medicine: FDA = Food and Drug Administration; ORA =- Office of Regulatory Affairs; NA = Not applicable.

SOURCES: [a]U.S. Congress, General Accounting Office, "Food Safety and Quality: Who Does What in the Federal Government," RCED-91-19B, December, 1990.
[b]The Center for Food Safety and Applied Nutrition, Food and Drug Administration
[c]The Center for Veterinary Medicine, Food and Drug Administration

Table 1O-2—FDA Domestic Inspection Activities, Selected Years

Year	Number of Inspections: FDA	Number of Inspections: State contract	Samples analyzed
1980[a]	16,243	NA	16,440
1985[a]	12,463	11,943	23,010
1988[a]	8,232	7,152	19,965
1989[a]	7,568	7,766	20,098
1990 [b]	7,054	7,031	20,849
1991[b]	9,195	7,633	20,780

NA - Not available

SOURCES: [a]U.S. Congress, General Accounting Off Ice. "Food Safety and Quality: Who Does What in the Federal Government," RCED-91-19B, December 1990.
[b]Food and Drug Administration, Office of Leglislative Affairs

In **addition** to cooperative agreements and State contracts, the FDA commission program provides authority to 367 State and local officials to assist the FDA in enforcing the Federal Food, Drug, and Cosmetic Act. This program uses State and local officials to perform specifically designated functions that are subject to Federal jurisdiction, such as conducting examinations. inspections, and investigations. The purpose of this program is to provide State officials with the authority to conduct inspections, review and copy records, and collect samples in FDA regulated establishments: in some States there is no other statutory authority for such inspections (18).

FDCA contains little specific preemption language regarding Federal versus State regulatory requirements. **Thus, FDA is not in a position to** oversee and approve State programs and employees. FDA does provide guidance and training to State agencies, evaluates State programs using national standards, and rates State officials for their competency, familiarity with, and uniformity in applying national standards within individual States (18).

Table 10-3—Food Service Establishments Covered by FDA-State Cooperative Inspection Programs, 1991

Food service establishments	636,000
Retail food stores	150,000
Food vending locations	1,090,000
Grade A milk farms	126,000
Milk pasteurization plants	724
Shellfish processors	770
Shellfish shippers	750
Shellfish growing areas	3,000

SOURCE. Off Ice of Legislative Affairs, Food and Drug Administration

In addition to its domestic responsibilities, FDA is mandated to ensure that imported products meet the same safety and labeling standards as domestically produced products. Field office personnel inspect imported food products at ports of entry and warehouses. Paperwork accompanying products subject to FDA regulation are reviewed to determine whether physical inspection is warranted. A physical inspection is conducted on those products suspected of being adulterated, misbranded. or otherwise in violation of the FDCA. The physical inspection ranges from a quick, visual examination of products at a wharf to sample collection and laboratory analysis (table 10-4) (18).

FDA Enforcement Activities

The FDA can issue written warnings to violators, request voluntary recall of violative food products. initiate seizures of violative food products, seek court-ordered injunctions, and seek criminal prosecutions. Warning letters[2] are issued by FDA only for violations of regulatory significance. Warning letters do not commit FDA to take an enforcement action if action is not taken to promptly correct violations. However, warning letters do contain specific notice that failure to promptly correct violations may result in enforcement action. The letters **usually** allow the company 15 working days to respond (table IO-5).

Imported products that fail to meet requirements must be exported, destroyed, reconditioned. or relabeled to bring them into compliance with Federal laws and regulations (table IO-6).

THE U.S. DEPARTMENT OF AGRICULTURE

The U.S. Department of Agriculture (USDA) is responsible for implementing a comprehensive system of inspection that ensures that meat, poultry, meat and poultry products, and selected eggs and egg products moving in interstate and foreign commerce are safe, wholesome, and correctly labeled and packaged. The USDA Food Safety **and inspection Service** (FSIS) is **responsible for** the safety, wholesomeness, and accurate labeling of meat

[2]Warning letters were implemented in 1991. Prior to that time, written warnings consisted of regulatory letters or notices of adverse findings. Regulatory letters were sent when FDA concluded that violations were serious enough to warrant seizure, injunctions, or criminal penalties against firms or individuals if corrective action was not taken. A notice of adverse findings was sent when FDA concluded that a violation was not serious enough to warrant immediate action against firms or individuals, but was serious enough to warrant some type of written notice (18).

Table 1O-4—FDA Import Inspection Activities, 1984-1991

Year	Wharf examinations	Samples examined
1984[a]	*26,200*	19,150
1985[a]	*28,800*	20,600
1986[a]	*35,650*	26,350
1987[a]	*33,040*	29,890
1988[a]	*38,760*	32,590
1989[a]	*63,006*	37,570
1990[b]	*39,112*	37,163
1991[b]	*43,769*	38,042

SOURCE: [a]U.S, Congress, General Accounting Office, ''Food Safety and Quality: Who Does What in the Federal Government," RCED-91-19B, December 1990.
[b]Food and Drug Administration, Office of Legislative Affairs.

and poultry products, and the Agricultural Marketing Service (AMS) is responsible for the safety of egg products.

Statutory Authority for USDA Inspection of Meat and Poultry Products

Statutory authority for meat and poultry product inspection is provided by the Federal Meat Inspection Act of 1906 (PL 59-242) as amended by the Wholesome Meat Act of 1967 (21 U.S.C. 601 et seq) and the Federal Poultry Products Inspection Act of 1957 (PL 85-175) as amended by the Wholesome Poultry Products Act of 1968 (21 U.S.C. 451 et seq).

For the purpose of regulation, meat food products are defined in part as

> **Any product capable of use as human food which is made wholly or in part from any meat or other portion of the carcass of any cattle. sheep, swine. or goats, excepting products which contain meat or other portions of such carcasses only in relatively small proportion or historicall, have not been considered by consumers as products of the meat food industry and which arc exempted from definition.**

The term meat products applied to food products of horses, mules, and other equines shall have a comparable meaning to that provided for cattle, sheep, swine, and goats (Section l(j)). Poultry is defined (Section 4(f)) as

> A **domesticated bird whether live or dead, and poultry product means any poultry carcass or part thereof. or any product which is made wholly or in part from any poultry carcass or part thereof, excepting products which contain poultry ingredients only in relatively small proportion or historically have not been considered by consumers as products of the poultry food industry.**

FSIS is responsible for the inspection of meat and poultry products. FDA is responsible for premarket approval of any food and color additives added to meat and poultry products, and for products that contain meat but that are not traditionally considered to be meat products (e. g., sandwiches with meat in the filling).

The Federal Meat Inspection Act and the Federal Poultry Inspection Act allow USDA to remove adulterated or misbranded products from the market. Adulterated meat and poultry products are those that contain poisonous or deleterious substances that may render the product injurious to health. In cases where such substances are natural, the product is not considered adulterated if the quantity of poisonous or deleterious substances in or on the product does not ordinarily render it injurious to health. For added substances, meat and poultry products are also

Table 1O-5—FDA Enforcement Activities, 1988-1991

	Regulatory letters		Recalls	
Fiscal year	Food and cosmetics	Animal drugs and feeds	Food and cosmetics	Animal drugs and feeds
1988	*36*	169	*470*	*54*
1989	*13*	*93*	*570*	*89*
1990	*24*	*166*	*725*	*62*
1991	*122*	123	**566**	91

	Seizures		Injunctions		Prosecutions	
Fiscal year	Food and cosmetics	Animal drugs and feeds	Food and cosmetics	Animal drugs and feeds	**Food** and cosmetics	Animal drugs and feeds
1988	121	17	6	2	13	5
1989	88	9	3	6	5	3
1990	78	9	4	3	5	3
1991	66	4	5	2	2	3

SOURCE: Food and Drug Administration, Off Ice of legislative Affairs.

Table 1O-6—FDA Import Enforcement Activities, 1988-1991

Fiscal year	Import samples analyzed: Food and cosmetics	Import samples analyzed: Animal drugs and feeds	Adverse findings[a]: Food and cosmetics	Adverse findings[a]: Animal drugs and feeds
1988	32,801	251	11,648	88
1989	37,936	189	14,294	73
1990	37,678	197	15,080	35
1991	38,147	148	13,487	38

[a]The number of analyzed samples that failed to meet established standards and policy guides, or would for other reasons support a regulatory action.

SOURCE: Food and Drug Administration, Office of Regulatory Affairs.

Table 1O-7—USDA Residue Testing in Slaughtered Animal Tissues, 1988-1990

Sample type	1988	1989	1990(est)
Food chemistry	70,021	*62,435*	**62,000**
Food microbiology	37,410	*36,908*	37,000
Chemical residues	102,714	*185,163*	185,000
Antibiotic residues	223,210	*255,851*	256,000
Pathology	11,160	11,017	11,000
Serology	3,928	1,630	1,600
Additives in nonfoods	12,007	10,907	10,900
Radiation	3,184	139	
TOTAL	*463,634*	*564,050*	*563,500*

SOURCE: General Accounting Office, compiled from the Food Safety and Inspection Service,

considered adulterated if they contain substances deemed unsafe by the appropriate meanings defined in the Food, Drug and Cosmetic Act (i.e., section 408 for pesticidal chemicals, section 409 for food additives, and section 706 for color additives).

Meat and poultry products are considered misbranded if among other things, the labels are false or misleading, if they are offered for sale under the name of another food, if they are an imitation of another food and the label does not clearly state so, if the container fill is misleading, and if label information required by law is not present.

FSIS Inspection Activities

Plans for meat and poultry plant facilities, equipment, and procedures must be approved by FSIS prior to operation or use to ensure that such operations will be sanitary. The floor plan, water supply, waste disposal systems, and lighting for each plant must be approved. Facilities and equipment must be easy to clean. In 1989, FSIS reviewed 3,851 blueprints of meat and poultry plants and 2,864 drawings of equipment. Once in operation, facilities and equipment are monitored for sanitation. Inspectors monitor operations in meat processing plants, and processing procedures and product formulations are reviewed to ensure that the products will be safe. Labels are checked for truthfulness and conformance with labeling laws and regulations (18).

All cattle, sheep, swine, goats, horses, mules, and other equines slaughtered for use as food must be inspected prior to slaughter at the slaughtering plant. Their carcasses also are examined after slaughter. Slaughtering cannot take place without the presence of an inspector, Veterinarians check the live animals for symptoms of disease or other abnormal conditions. After slaughter, inspectors under the supervision of veterinarians, examine each carcass and internal organs for symptoms of disease or contamination that would make all, or part, of the meat unfit for human consumption. Animal tissues may also be analyzed for drug and chemical residues to ensure that they meet tolerances as established by FDA (animal drugs) or EPA (pesticides) (table 10-7).

FSIS interprets its inspection mandate to apply to species and not breeds. The offspring of two breeds of the same species, such as Hereford and Angus beef cattle, would be classified as beef and amenable to inspection. The hybrid offspring of two different species, however, may or may not be inspected depending on which parent the offspring physically resembles. For example, the offspring that results from crossing a cow and a buffalo will be amenable if it resembles the cow, but not amenable, and therefore not subject to mandatory inspection, if its physical appearance is that of a buffalo (15). The slaughter of experimental animals at official establishments is not allowed unless certain conditions are met. These conditions include statements from FDA, EPA, or the Animal and Plant Health Inspetion Service (USDA-APHIS) that experimental drugs, chemicals, or biological have been used in accordance with regulations and are below tolerances (9 CFR 309.17 and 381 .75).

FSIS is developing methods to streamline inspection activities based on hazard assessment and using statistical sampling methods, a system known as the Hazard Analysis Critical Control Point (HACCP). The agency currently is conducting a study to determine the most effective way to implement the HACCP system into meat and poultry inspection, and is working with industry to develop model HACCP plans and is soliciting volunteer plant participation to develop the pilot program. Workshops have been or will be held for application of HACCP to minimally processed foods that are refrigerated, cooked sausage, fresh ground beef, young chicken slaughter, and market hog slaughter.

Table 1O-8—FSIS Inspection Staff, 1988-1990

Program area	Staff years 1988	1989	1990 (est)
Slaughter inspection	6,969	7,004	7,042
Processing inspection	2,847	2,791	2,805
Import-export inspection	230	231	232
Laboratory services	384	373	376
TOTAL	10,430	10,399	10,455

SOURCE: General Accounting Office, compiled from the Food Safety and Inspection Service.

Table 1O-9—AMS Inspection Activities, 1988-1990

Activity	1988	1989	*1990* (est)
Egg products inspected (billion lb)	1.7	1.6	1.6
Egg product plants	86	83	86
Egg handler surveillance visits	9,723	8,769	8,200
Lab samples analyzed			
Food chemistry/ microbiology	46,481	40,969	42,000
Chemical residues	384	517	500

SOURCE: General Accounting Office, compiled from the Agricultural Marketing Service.

FSIS also inspects imported meat and poultry products to ensure that they meet the same standards as domestic products. Countries wishing to export to the United States must impose inspection requirements at least equal to those enforced in the United States. FSIS evaluates the inspection programs of these countries to determine eligibility and reviews the way the systems are operated. As of the end of 1989, 1,431 plants in 34 countries were certified to export meat and poultry products to the United States. FSIS also reinspects imported meat and poultry products, on a sample basis, when they enter the United States.

FSIS is responsible for inspecting and monitoring about 6,720 meat and poultry plants throughout the United States, and 220 official import establishments. FSIS employs approximately 7,800 Federal inspectors of which 6,050 are food inspectors, 180 are food technologists, and 1,050 are veterinarians (table 10-8). Between 1980 and 1989 funding declined by 3 percent (in constant 1989 dollars) and staff years declined by 6 percent. However, during this same time period, inspection activities increased considerably. Pounds of processed poultry inspected increased by 134 percent, pounds of slaughtered poultry inspected increased by 52 percent, and samples analyzed increased by 182 percent. Compliance reviews also increased by 45 percent (18).

FSIS monitors State programs for inspecting meat and poultry products that will be sold only in the State in which they are produced. State programs are required to beat least equal in rigor to Federal programs. About half of the States conduct their own meat and poultry inspections and about 5,700 plants are inspected by State programs. FSIS is authorized to reimburse these programs for up to 50 percent of the inspection costs. FSIS provided about $36.5 million in grants to 28 States in 1989. If States abolish their inspection programs, FSIS is required to assume inspection responsibility (18).

AMS Inspection Activities

Agricultural Marketing Service (AMS) activities are primarily related to food quality rather than food safety issues. AMS establishes standards of quality and grades for dairy, egg, fruit, poultry, and vegetable products (see ch. 14). Food safety responsibilities are in the area of egg products and shell egg surveillance programs. Statutory authority is granted by the Egg Products Inspection Act as amended (21 U.S.C. 1031 et seq).

The Egg Products Inspection Act requires continual USDA inspection of all egg products processing plants. For the purpose of regulation, egg products are defined as liquid, frozen, and dried egg products. Further processed products, such as noodles and custards, which contain egg products but have not been considered as products of the egg food industry, are not subject to inspection by USDA (but are subject to FDA authority). Facilities, equipment, and methods of processing are inspected for cleanliness and the ability to perform intended functions. Inspections include visual evaluations and laboratory tests. Egg products can be analyzed for microbial and chemical residues and other contaminants (table 10-9) (18).

The Egg Products Inspection Act also requires mandatory quarterly inspections of shell egg handlers who pack eggs for consumer sales, and restricts certain types of shell eggs from moving into consumer channels. Restricted eggs include checked eggs (those with cracked shells that are not leaking); dirty eggs (which may be sent only to official USDA inspected processing plants for proper handling and processing); incubator rejects (infertile or unmatchable eggs); leakers (cracked eggs with contents leaking); and inedible and loss eggs (unfit for human consumption). Inedible eggs and egg products

Table 1O-10—AMS Enforcement Activities, 1989

Penalty	Cases closed
Letter of information	197
Letter of warning	86
Closed without penalty	21
Criminal prosecution	1

SOURCE: General Accounting Off Ice, complied from the Agricultural Marketing Service.

must be denatured and destroyed or otherwise handled to preclude their use as human food.

AMS has cooperative agreements with all 50 States, Puerto Rico, and the Virgin Islands. AMS uses State inspection personnel to make unannounced quarterly shell egg surveillance visits to shell egg-packing establishments. AMS provides Federal oversight for State programs, and reimburses States for performing surveillance inspection work. In 1989, approximately 1,500 shell egg-packing plants and 500 hatcheries were subject to, and received, quarterly inspections by USDA or cooperating State agencies (18).

Egg products may be imported only from countries with egg products inspection systems that meet the standards of the U.S. system. As of September, 1989 only Canada and the Netherlands met this requirement. AMS monitors incoming products and routinely tests products for *Salmonella* and various environmental contaminants. Shell eggs are imported for use in producing egg products and are processed under continual inspection. Table 10-10 summarizes AMS enforcement activities for 1989.

APHIS Inspection Activities

The Animal Plant Health Inspection Service (APHIS) has few legal responsibilities to protect or promote food safety and quality unless the organisms or chemicals of concern to public health are also of concern to animal or plant health. Programs designed to protect the animal industry against pathogens or diseases that can also pose foodborne risks to humans improves food safety. In 1990, for example, APHIS instituted an emergency program to combat *Salmonella enteritidis* in poultry. APHIS tests and monitors all egg type breeding and multiplier flocks as well as controls the interstate movement of poultry, eggs, and material from known culture positive flocks and exposed flocks. APHIS also conducts programs to prevent communicable disease of foreign origin from entering the United States, diagnoses foreign animal diseases should they enter the country, and prevents the spread of disease through interstate shipments of livestock.

APHIS also regulates animal biologics under the Virus-Serum-Toxin Act (21 U.S.C. 15 I-158) A veterinary biologic is any natural or synthetic virus, serum, toxin, or microorganism intended for use in the diagnosis, treatment, or prevention of animal diseases. USDA and FDA have a standing committee to determine whether a new animal product is a drug or a biologic. Under FDCA (21 U.S. C. 351 -360b, 1982) FDA has jurisdiction to regulate new animal drugs that are not biologics.

Outside Input Into the USDA Decision Process

Statutory authority for USDA food safety regulatory activities does not require public notification and comment, except for new food additives used in meat and poultry products that are subject to notice and comment procedures with FDA. USDA (most notably APHIS) has undertaken a voluntary notification program for the environmental release of genetically modified organisms. USDA does use advisory committees to provide outside expertise to aid their regulatory decisions (16).

THE ENVIRONMENTAL PROTECTION AGENCY

The Environmental Protection Agency (EPA) is responsible for regulating all pesticide products sold or distributed in the United States. For the purpose of regulation, EPA defines a pesticide as any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, and any substance or mixture of substances intended for use as a plant regulator. defoliant, or desiccant. A pest is defined as 1) any insect, rodent, nematode, fungus, weed, or 2) any other form of terrestrial or aquatic plant or animal life or virus, bacteria, or other microorganism (except viruses, bacteria, or other microorganisms on or in living man or other living animals) that the administrator declares a pest (7 U.S. C. 136(2)(t)).

Statutory Authority for EPA Food Safety Regulations

Statutory authority for the regulation of pesticides are provided by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) of 1947 (7 U.S.C. 136 et seq), and the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq).

Under FIFRA, EPA registers new pesticide products, reregister existing pesticides, specifies the terms and conditions of their use, and removes hazardous pesticides from the market. (See ch. 7.) Under FIFRA, EPA can register a pesticide only if it determines that the pesticide, when used according to directions, will perform its intended function without causing any unreasonable risk to humans or the environment, taking into account the economic, social, and environmental costs and benefits of the pesticide's use.

Under FDCA, EPA has responsibility for determining the safety of pesticide residues in or on food for humans, or feed for domestic food animals. Before a pesticide can be registered for use on a food or feed crop, a tolerance, or an exemption from the requirement of a tolerance, must be established. A tolerance is the maximum level of pesticide residues that can be present in or on raw agricultural commodities, food, or feed transported in interstate commerce. Tolerances, or exemptions from the requirement of a tolerance, must be established for each active and inert ingredient contained in the pesticide, and for each raw commodity, processed commodity, and livestock species that might contain residues of the pesticide.

Any person applying for a pesticide registration may file a tolerance petition. Appropriate data must be submitted so that EPA can define a safe and realistic tolerance level, or grant the exemption. These data include information on the pesticide's toxicity (potential to cause adverse health effects), the residues that may remain in or on food or feed, and an analytical method that can detect the chemical and any metabolizes of concern in the commodity (19).

In addition, EPA has discretionary authority to establish tolerances and exemptions on its own initiative or in response to a request of any interested person. EPA can set a tolerance, grant an exemption from tolerances, or amend a current tolerance if the current pesticide registration is changed. At the request of FDA or USDA, EPA also recommends enforcement levels (action levels) for residues that may occur in food and feeds resulting from other than direct application of the pesticide to the crop. For example, a pesticide may persist in the environment even after a pesticide registration has been canceled.

Section 408 of the Federal Food, Drug, and Cosmetic Act (FDCA) provides the authority to establish tolerances for raw agricultural commodities, and section 409 provides the authority for processed products. Section 408 was first passed in 1954, and section 409 was passed 4 years later. Initially, tolerances for pesticide residues were established by the Food and Drug Administration, but with the creation of the Environmental Protection Agency in 1970, these pesticide regulatory responsibilities were transferred to the EPA.

Raw agricultural commodities are considered to be fresh fruits, vegetables, grains, nuts, eggs, raw milk, and meats. The term excludes foods that have been processed, fabricated, or manufactured by cooking, freezing, dehydration, or milling among other processes (40 CFR 180. l(e)). When establishing pesticide residue tolerances on raw agricultural commodities, EPA must not only consider the safety of the product, but also the necessity of the pesticide to produce an adequate, wholesome, and economical food supply; other ways that the consumer may be affected by the pesticide; and the usefulness of the pesticide. Under FDCA, raw agricultural commodities that contain pesticide levels above established tolerance levels are considered adulterated (21 U.S.C. 346a (a)(b)).

The tolerance established for the raw commodity also applies to the processed food product if the pesticide residue level in the processed product is less than that tolerance level. If, however, the processing concentrates the pesticide residue such that levels contained in the processed food exceed the established tolerance for that pesticide in raw commodities, then a separate tolerance must be established for the pesticide in the processed food. The tolerance that then must be established for the processed food is considered a food additive under FDCA. Food additive petitions do not include an assessment of the benefits that may result from the pesticide, The Delaney Clause of the food additive amendment prohibits the use of carcinogenic food additives.

Outside Input Into EPA Decision Process

Under FIFRA, EPA is required to publish notice of the receipt of a pesticide registration application or of any Experimental Use Permit (EUP) that is of regional or national significance. EUP's are required before pesticides can undergo field trials. Trials involving less than 10 acres of land or 1 surface acre of water, and for which the crop is destroyed or used only for research (i.e., it is not used for food or feed) are generally not required to file an EUP, however. Notifications are published in the Federal Register and the public has 30 days to provide written comments. EPA also publishes the issuance of pesticide registrations and EUP's. If public comments indicate that there is sufficient interest or that it would otherwise be in the public interest, EPA can hold a public

Table 10-1 l—Selected State Pesticide Enforcement Activities, 1988-1990

Activity	1988	1989	1990 (est)
Use inspections	12,639	19,308	18,829
Producer establishment inspections	1,488	1,662	2,509
Marketplace inspections	5,662	8,032	4,035
Import inspections	273	431	475

SOURCE: General Accounting Office, compiled from the Environmental Protection Agency.

hearing concerning an application. EPA can also use advisory committees and generally tries to include public representatives on these committees. EPA tries to draw a distinction between private citizens and representatives of public interest groups (40 CFR 25 .7(c)(1)(i and ii). EPA can also utilize its FIFRA Scientific Advisory Panel as a forum for scientific peer review and comment. Panel meetings are public and allow an opportunity for public comment.

EPA Enforcement Activities

EPA does not enforce tolerances; that is the responsibility of USDA and FDA, and State enforcement agencies. USDA has monitoring and enforcement responsibilities for pesticide residues in meat, poultry, and egg products. FDA is responsible for monitoring the rest of the Nation's food supply. These agencies test samples of food to determine if the food contains residues for which no tolerance has been set or residues exceeding tolerance levels, rendering the food adulterated. Food commodities with residues in excess of tolerance levels or residues for which no tolerance has been set are subject to seizure. EPA has cooperative agreements with the States to perform enforcement activities. State agencies conduct use inspections, inspect pesticide-producing establishments, maintain marketplace surveillance, inspect imports, and inspect dealers and users of restricted-use pesticides. They also complete analyses of pesticide samples collected during inspections (table 10-11) (18).

Similar to other Federal agencies, resources devoted to food safety activities at EPA declined during the 1980s. EPA had 17 percent less staff and 8 percent less funding in 1989 compared to 1980 (17).

OTHER FEDERAL AGENCIES

Other Federal agencies also carry out activities that have some effect on food safety. The National Marine Fisheries Service (National Oceanic and Atmospheric Administration (NOAA), U.S. Department of Commerce) conducts voluntary seafood inspection programs. The Agricultural Marketing Act of 1946(7 U.S.C. 1621 et seq) authorized the Secretary of Agriculture to establish a voluntary inspection and certification program for agricultural products including fish and shellfish traded in interstate commerce. The act also required the Secretary to conduct research and development on methods of processing, packaging, handling, storing, and preserving products, and to develop and improve standards of quality, condition, quantity, grade, and packaging to encourage uniformity and consistency in commercial practices. The Fish and Wildlife Act of 1956(16 U.S.C. 742a et seq) transferred USDA functions and authorities pertaining to commercial fisheries, including the voluntary seafood inspection program, to the U.S. Department of the Interior in 1958. Reorganization Plan No. 4 of 1970 transferred the functions described in the Fish and Wildlife Act to NOAA. The National Marine Fisheries Service (NMFS) conducts the National Seafood Inspection Program and the Product Quality, Safety and Identity Research Program (18).

The seafood inspection program is voluntary and fee based. Plants and fishing vessels are inspected for sanitation and certified. Seafood products are analyzed for microbial and chemical contamination, for decomposition, and for species identification. NMFS has cooperative agreements with the States and provides training to State inspectors who are certified to perform inspection activities. NMFS also monitors State inspection activities. NMFS does not provide Federal grants to States for providing inspection services, but does reimburse States for costs incurred at an agreed on hourly rate (18).

In February, 1991 the FDA established a new Office of Seafood (within CFSAN). This office will cooperate with NMFS and will increase FDA responsibilities for seafood inspections. The office will oversee seafood inspection programs by FDA in cooperation with NMFS and State agencies, oversee the development of training programs for FDA, State, and local inspectors, and increase research and develop methods to detect and evaluate the effects of microbial and chemical contaminants in seafood that might pose public health hazards (11).

As of January 1990, there were 144 NMFS inspectors, 63 NMFS cross-licensed Federal (USDA) inspectors, and 74 NMFS cross-licensed State inspectors. It is estimated that there are approximately 1,878 fish processing plants in the United States, and about 141 of those contracted for inspection services (table 10-12) (18). FDA has about 300 people engaged in various seafood safety programs

Table 10-12—National Marine Fisheries Inspection Activities, 1981-1989

Year	Laboratory testing			Total
	Microbial	Chemical	Physical	
1981 ... , ... , ...	75	35	5	115
1982	69	28	7	104
1983	70	6	2	78
1984	71	7	6	84
1985	39	9	11	59
1986	43	23	5	71
1987	51	20	14	85
1988	68	22	15	105
1989	33	25	8	66

SOURCE: General Accounting Office, compiled from the National Marine Fisheries Service.

and is expected to add another 270 scientific and inspection positions within 2 years (1 1).

Other Federal agencies with some food safety activities include the Agricultural Research Service (USDA-ARS), which conducts food safety research primarily to develop methods to detect and control bacterial and parasitic contamination of meat and poultry and their products. ARS develops methodologies to detect chemical residues in meat and poultry and their products, and methods to detect and prevent mycotoxins in plant commodities.

The Public Health Service Act (42 U.S.C. 201 et seq) authorizes the Center for Disease Control (Department of Health and Human Services) to conduct research on, and monitor and control foodborne diseases.

The Federal Trade Commission Act (15 U.S.C. 51 et seq) authorizes the Federal Trade Commission (FTC) to investigate advertising claims that may result in unfair competition and unfair or deceptive acts and practices in commerce. Under this Act, the FTC has investigated claims of companies that test fresh produce for pesticide residues, health claims for food products, and home test kits for food impurities.

The U.S. Customs Service assists FDA, USDA, and EPA in their import inspection duties. It makes sure that documentation is in order and, via a memorandum of understanding with FDA, delivers samples of imported food products to FDA on request.

The Bureau of Alcohol, Tobacco, and Firearms (BATF) regulates production and distribution of alcohol and tobacco products. FDA has responsibility for safety of alcoholic beverages; however, a memorandum of understanding with BATF gives most of that responsibility to BATF.

The Federal Grain Inspection Service (USDA) inspects corn, sorghum, and rice for aflatoxin contamination.

FOOD SAFETY COORDINATION AMONG FEDERAL AGENCIES

Given that so many agencies are involved in various aspects of food safety, coordination between the agencies is imperative. In general, this coordination involves notifying appropriate agencies of findings that may indicate that regulations have been violated, and trying to avoid inspection duplication when products or facilities are under the jurisdiction of more than one agency. In 1989, FDA had 27 memorandums of understanding relating to food safety and quality with other Federal agencies, primarily USDA.

EPA, FDA, FSIS, and AMS all have agreements to notify each other in the event that residues from drugs, pesticides, or environmental contaminants exceed tolerance levels. EPA is to notify FDA and USDA of any pesticide use it encounters that may have resulted in residues that adulterate human food or animal feed. FDA is to notify EPA of possible misuse of pesticides or chemical substances that may indicate a violation of EPA laws; and to notify USDA of illegal residues of drugs, pesticides, or environmental contaminants in human food or animal feed. USDA is to notify FDA of findings of illegal residues in edible meat, poultry, or egg products and to keep FDA and EPA informed of all FSIS and AMS sampling and testing programs for illegal residues (18).

FSIS, AMS, and FDA try to avoid duplicating inspections and exchange information on violative conditions concerning food manufacturers whose facilities are under the jurisdictions of more than one agency. For example, the Egg Products Inspection Act gives AMS authority over egg product plants, egg producers and packers, other firms engaged in marketing eggs including hatcheries, and imported egg products. FDA has jurisdiction over restaurants, institutions, food manufacturing plants, and other similar establishments that break and serve eggs or use them in their products. The National Marine Fisheries Service covers fishery products plants that are under NMFS voluntary inspection contracts and also subject to FDA inspection. NMFS is to apply to these plants FDA regulations concerning good manufacturing practices, labeling, food additives, tolerances, standards of identity, minimum quality, and fill of container. NMFS also cross-licenses FDA and USDA inspectors for seafood inspections. The agencies notify each other of violations (18).

INTERPRETATION OF FEDERAL FOOD SAFETY LAWS WITH RESPECT TO PRODUCTS PRODUCED WITH BIOTECHNOLOGY

None of the laws used to regulate food safety contain specific provisions for products derived using biotechnology. However, based on the Coordinated Framework (see ch. 7), all of the Federal agencies involved in food safety regulation feel that current laws are adequate to cover products created with biotechnology techniques and that no new regulation is needed for such products. The broad interpretation of the existing statutory authority allows for the agencies to extend their regulatory authority to cover genetically modified products.

FDA Regulation of Biotechnology-Derived Food Products

The application of the Federal Food. Drug, and Cosmetic Act to the regulation of food products produced with biotechnology is complex. FDA must choose a regulatory **course** that ensures public safety, however, unnecessary over-regulation could damage agricultural competitiveness and deny new products to consumers. FDA's statutory authority should be implemented in a manner consistent with past actions, with the goals of the Coordinated Framework, and with FDA's own stated policy that it will regulate the product and not the process. FDA must apply its authority to biotechnology products in such a way that they capture those foods for which there are safety concerns. but it is important that it do so in such a way that a regulatory structure that requires review of all new food crop varieties is not established. Finding an appropriate balance is a complex task.

As discussed earlier, FDA has the legal authority to take action against foods adulterated with poisonous or deleterious substances that would ordinarily(for inherent natural substances) or may (for added substances) render the food injurious to health. Action can also be taken against foods containing an additive(s) for which no regulation exists or that is not GRAS for its intended use. Because FDA does not generally conduct a premarket safety evaluation of food. only of food additives. some groups (e. g., the Environmental Defense Fund) feel that use of the adulteration clauses to remove marketed food products made from biotechnology is inadequate to ensure the safety of these foods and have proposed that essentially all food products produced with biotechnology be classified as food additives. FDA is faced with the challenge of deciding whether new biotechnology-derived food products are GRAS or whether they are food additives that require premarket approval.

The types of food products likely to be developed using biotechnology include

- single compounds (e. g., flavors, enzymes, colors) produced by genetically modified organisms (e. g., bacteria, cell culture) and added to goods,
- genetically modified organisms (e. g., yeast and bacteria) that become part of the food itself (e. g., dairy, meat, and vegetable starter cultures),
- simple mixes of compounds added to food, and
- whole foods (transgenic crops) (8).

Biotechnology-derived food products in the first three categories generally fit the standard interpretation of a food additive and thus may be regulated in the same manner as additives produced by conventional means. Thus. genetically modified starter cultures and single and simple mixture compounds derived from genetically modified organisms may be treated as food additives it the modification alters the ingredient in such a way that it is no longer GRAS (8, 9. 12).

The primary difficulty FDA will have in applying its statutory authority to food products produced with biotechnology will be with respect to whole foods (e. g.. transgenic crops). New varieties of crops have generally been regarded as safe (GRAS) by FDA. and thus have not required pre,arket approval as a food additive. FDA has the option of similarly allowing biotechnology-derived whole foods to be marketed, relying on its seizure procedures to remove products for which safety risks arise. or of applying the food additive definition to whole foods produced with biotechnology. In the latter case. biotechnology products either would be affirmed as GRAS or declared a food additive requiring premarket approval. The question that arises with biotechnology is does the process alter the food in such a way that it is now adulterated or is no longer GRAS'?

Use of the Seizure Procedures

It is possible to use biotechnology to create transgenic crops that contain completely novel gene products. However, it is also quite possible to use biotechnology to create transgenic crops essentially equivalent to new varieties produced by traditional means. New varieties produced by conventional methods do not undergo premarket evaluation. Rather. FDA relies on their ability to seize products should a food safety problem arise. FDA could

apply a **similar approach** to whole foods produced with biotechnology.

As is currently the case, whole foods produced with biotechnology that contain poisonous or deleterious substances could be considered adulterated if the substance is in sufficient quantities that it *would ordinarily render* the food injurious to health (inherent natural substances) or *may render* the food injurious to health (added substances). Added substances include those present as a result of human intervention (e. g., mercury in fish). Broadly interpreted, added substances could include inherent naturally occurring substances whose levels have been significantly altered as a result of human intervention. Such an interpretation could include new crop varieties produced by conventional breeding procedures, as well as whole foods produced with biotechnology methods. The use of traditional breeding methods to develop new crop varieties have generally not been found to alter the product in such a way that they would be considered adulterated. Given that many biotechnology products will be essentially equivalent to new products produced conventionally, the application of seizure standards to whole foods derived from biotechnology must be implemented in a manner that captures products for which there are safety concerns without establishing a regulatory structure that requires the review of all new food crop varieties (7, 9).

An advantage of using the seizure procedure to remove biotechnology-derived whole foods from the market is that this procedure does not a priori impose an extensive regulatory process and premarket approval for all foods for which biotechnology has been used. Action is initiated against those products that clearly pose a health risk to society. This procedure is the one currently applied to whole foods produced with conventional methods. Like biotechnology, conventional breeding can alter the levels of toxic substances or nutrients in whole foods.

A disadvantage of relying on seizure procedures to remove biotechnology-derived whole foods from the market, is that action is not initiated until a product poses a health safety risk, and/or someone is adversely affected. This is no different than what occurs now with conventionally produced whole foods, but given that biotechnology is a new procedure, and there appears to be public apprehension concerning this technology, removal of an unsafe biotechnology product from the market could be very damaging to public acceptance of biotechnology in food production.

Use of the Food Additive Definition

FDA could choose to apply the food additive definition to whole foods, including those produced by biotechnology or conventional methods. Recall that a food additive is any substance whose intended use may be reasonably expected to directly or indirectly become a component or otherwise affect the characteristics of any food, unless the substance is GRAS or subject to some other exemption of the food additive amendment (e. g., pesticides, color additives, etc.).

Application of the food additive definition to whole foods requires a specification of what food ingredient actually is the food additive. A whole food could be classified as a food additive if that food is used as an ingredient in another food product. For example, carrots used in beef stew could be considered a food additive if the carrots are not GRAS. Alternatively, some trait or constituent of the food could be designated as a food additive, if that constituent is not GRAS.

Because of a long history of safe use prior to 1958 when the food additive amendment was enacted, most whole foods have been considered GRAS. Likewise, FDA has generally not required a formal review to establish GRAS status of new varieties of crops produced after 1958 because changes resulting from traditional breeding have generally been felt not to result in traits that are sufficiently different to warrant such a review. A significant issue with respect to whole foods produced with biotechnology methods is whether these procedures alter the food in such a way that these products cannot now be viewed as GRAS.

Alternatively, constituents of whole foods could be designated as food additives if these constituents are not GRAS. Thus, for example, gene products resulting from biotechnology procedures could be classified as food additives. It is possible to transfer truly novel genes to whole foods. These genes may produce proteins that have previously not been part of the food system. Such expression products would not have been previously designated as GRAS, and would be good candidates for designation as food additives. However, many genes transferred between crops may code for proteins that are currently consumed. Under what circumstances will these proteins be deemed sufficiently different from those being consumed to warrant a formal review of GRAS status"? FDA could describe the kinds of traits that might be different enough to warrant review. Minor alterations of previously consumed proteins or the addition of common kinds of nontoxic proteins could potentially be viewed as not

raising sufficient concerns to warrant a formal review of GRAS status.

An advantage of declaring whole foods or traits contained in whole foods as food additives is that this affords an opportunity to examine these products prior to marketing. A disadvantage is that in some cases it may be technically difficult to actually conduct the safety assessment (see ch. 11). Additionally, if most or all biotechnology-derived whole foods are declared food additives, and conventionally produced products are not, it would behoove FDA to explain the scientific justification for such a distinction. Otherwise it could appear that FDA is regulating by process, which it has stated it will not do.

Other analysts have suggested different interpretations of the food additive amendment with respect to whole foods derived from biotechnology. One proposal is to apply the food additive definition to gene products that would have been classified as food additives if added to foods, and to exclude from the definition gene products that result in changed agronomic traits (8). As noted above, others have suggested that all whole food produced with biotechnology be classified as food additives with the possible exception of transgenic crops that could have been developed using traditional means rather than biotechnology (i.e., the genes transferred come from species that are sexually compatible with the host plant) (3). Still others have suggested that legal difficulties may arise in developing an approach to regulating whole foods produced with biotechnology that is risk based and not process based, without simultaneously establishing regulations that require formal review of all new crop varieties produced by conventional means (7).

Current Status of FDA Regulations

Given the complexities involved, and the controversial nature of genetically engineered food products, FDA policy has been a long time in the making. A clear policy statement and guidelines have been needed. The lack of a clear policy has been confusing to industry and the public. Many biotechnology-derived food products, including whole foods, are no longer in the preliminary stages of development; products are rapidly approaching commercialization. FDA no longer has the luxury of delaying a decision on whether or how they intend to regulate food products produced with biotechnology.

In May 1992, FDA released a preliminary policy statement regarding new varieties of crops produced with biotechnology (5). The policy statement is not final; public comments are being solicited. Some public interest groups oppose the policy and are threatening to take legal action to stop it. Thus, policy regarding the food safety regulation of transgenic crops is still evolving.

FDA policy states that it is the characteristics of the product, not the method used that will be of most concern. The FDA will not a *priori* require a food additive petition for all genetically modified whole foods. Rather, FDA will require an assessment of the expression products of the genetic modification and any unexpected or unintended effects that may result from genetic modification. Expression products that differ substantially in structure, function, or composition from substances found currently in the food supply may require a food additive regulation. New products that are not substantially different from foods currently consumed may, like new varieties conventionally produced. be considered as GRAS.

FDA policy emphasizes safety assessment guidelines that focus on determining whether the new plant varieties are as safe and as nutritious as their parental varieties. FDA is concerned that new toxicants not be introduced into the food supply, that the level of toxicants inherently present in foods is not unintentionally increased to levels exceeding those already consumed, that the composition or bioavailibility of nutrients is not significantly altered, and that compounds that are known to cause allergic responses in sensitive individuals are not transferred between crop varieties. Effects of processing on the composition of the food product must also be considered.

Decision trees are provided in the policy statement to assist firms in assessing the safety of genetically modified varieties. Characteristics of the genetically modified varieties are based on the characteristics of the host and donor species, the identity and function of the newly introduced substances, and any unexpected or unintended effects that may accompany the genetic change are emphasized. The safety assessment focuses on:

- toxicants known to be characteristic of the host and donor species,
- potential that food allergens will be transfered from one food source to another,
- concentration and bioavailibility of important nutrients for which the food crop is ordinarily consumed,
- the safety and nutritional value of newly introduced proteins, and
- the identity, composition, and nutritional value of modified carbohydrates, fats, and oils (5).

FDA states in their preliminary policy that if genetic modification does not result in the introduction of new

toxicants to the food supply, does not alter the level of toxicants already present, does not alter the composition or bioavailability of nutrients in new varieties, and does not result in the transfer of allergenic components to new varieties, then the new variety can be considered as equivalent to traditional varieties when used in a similar manner. If that traditional variety is classified as GRAS, then the new variety would also be GRAS. Modifications that result in varieties that contain new toxicants or significantly elevated levels of inherent toxicants are unacceptable. Modifications that result in nutritional changes or potentially increase the possibility of allergic reactions must be further evaluated by FDA. Such varieties may require a food additive petition and a complete premarket safety assessment.

FDA is also not requiring generic labeling of all new crop varieties produced with biotechnology methods. Approved products that may have altered nutritional composition or that contain compounds that are potentially allergenic may need to be labeled as such. Prior to commercialization, many transgenic crops will undergo field trials. Permits for such trials are granted by USDA and EPA and require an environmental assessment. FDA intends to coordinate with these agencies to prevent duplication in FDA's efforts to comply with NEPA.

FDA has not yet formally been petitioned to review a transgenic plant, although it has been asked to give an advisory opinion on the use of the kanamycin resistance gene as a marker in transgenic tomatoes, cotton, and rapeseed (6). FDA has also been asked to give an advisory opinion on the use of the antisense technology to delay softening in tomatoes. The agency has recently provided for public comment its response to this request.

FDA has ruled on an enzyme (chymosin) produced by a genetically modified bacteria, and used to clot milk in cheese production. Chymosin will be used to replace rennet, a GRAS enzyme extracted from the forestomachs of cattle. The manufacturers of chymosin sought a formal affirmation of the GRAS status of this enzyme. After reviewing the structure, function, and purity of the enzyme, and published information, FDA affirmed GRAS status for chymosin (4).

FDA Regulation of Biotechology-Derived Animal Drugs

All new animal drugs, whether administered directly to livestock or added to their feed, are required to receive premarket approval. Thus, biotechnology-derived drugs will undergo a premarket evaluation similar to that required for their traditionally developed counterparts. There is no difficulty in interpreting FDCA with respect to these products.

Transgenic crops used to feed livestock will face many of the same ambiguities as transgenic crops used as human food as discussed above. Transgenic animals that produce human or animal drugs may also raise questions concerning the safety of food products produced from these animals.

FSIS Regulation of Biotechnology-Derived Meat and Poultry Products

FSIS will regulate biotechnology in meat and poultry products. Food additives produced by fermentation using genetically engineered organisms and added to the meat, and genetically engineered meat starter cultures are classified as GRAS or food additives and are regulated as such. FDA is the agency responsible for approving the safety of these products and all food additives; FSIS will then consider approval of their use in meat and poultry products. These classes of biotechnology products will be handled in the same way that their conventional counterparts are (i.e., as food additives unless granted GRAS status). FSIS will also enforce the tolerances of biotechnology-produced pesticide and animal drugs in meat and poultry products as established by EPA and FDA.

Application of the Federal Meat Inspection Act and the Federal Poultry Inspection Act to transgenic animals is a little more ambiguous. FSIS is in the process of developing guidelines regarding transgenic animals. They are expected to issue guidelines concerning the slaughter of experimental livestock in which the attempts to insert foreign genes failed. Development of guidelines for transgenic livestock are in the preliminary stages and are not likely to be available any time soon. FSIS has indicated that it regards transgenic animals as new breeds, rather than new species, and thus they are amenable to inspection (1, 13, 15).

EPA Tolerances for Biotechnology-Derived Pesticides

EPA is responsible for establishing pesticide tolerance levels for, or exempting from the requirement of tolerances, any pesticides used in food and feed products. When an application is made under FIFRA to register a pesticide that will be used on agricultural commodities

marketed as food or feed, the applicant must also submit to EPA a petition proposing either the issuance of a regulation establishing a tolerance or an exemption of the pesticide from the requirement of a tolerance as required by FDCA (21 U.S. C. 346a). The trigger for establishing a pesticide tolerance for biotechnology products will be whether or not the biotechnology product is classified as a pesticide under FIFRA and has food or feed uses. Thus, EPA's role in food safety issues involving biotechnology products hinges on its interpretation of FIFRA with respect to these products (see ch. 7).

Responsibility for Transgenic Finfish and Shellfish

Finfish and shellfish have been identified that produce toxins highly poisonous to humans. Additionally, several species of seafood consumed by humans are known to concentrate environmental toxins and microbial toxins that may pose food safety risks to humans. At present it is not known how genetic engineering might affect these characteristics. Fish and seafood consumption in the United States has increased significantly, and transgenic finfish and shellfish are in varying stages of development. The FDA Office of Seafood has claimed food safety responsibility for transgenic fish and seafood products.

INTERNATIONAL COORDINATION

Because food is internationally traded and several nations are developing the capability of producing biotechnology-derived foods, there is a need to develop acceptable international standards for these food products. Several European countries as well as Canada and Japan are developing regulatory guidelines for the safety assessment of foods produced with biotechnology. Additionally, international organizations such as the Food and Agricultural Organization (FAO), the World Health Organization (WHO), and the Organization for Economic Cooperation (OECD) among others, are exploring the issues involved. The FAO and the WHO jointly consulted on the issue of food safety. They stated that any food safety assessment of biotechnology-derived foods should be based on sound scientific principles, that the extent of the evaluation should be based on potential risks, and that the evaluation should be multidisciplinary and include all steps in the production process.

Building on the FAO-WHO approach, the OECD, a group of industrial nations including Europe, the United States, Canada, Japan, Australia, and New Zealand, has established various working groups to discuss issues surrounding the development of products produced with biotechnology. With respect to food safety, OECD has established a group of international experts in the area of biotechnology safety to address issues related to food safety. Issues to be addressed include:

1. the scientific principles that underlie the definition of a new food or food component,
2. identification of methods to distinguish between new foods or food components and their conventional counterparts,
3. establishing whether conventional food and food components and their associated safety judgments are good benchmarks for assessing the safety of new foods or food components,
4. determining methods for establishing the substantial equivalence of the new foods or food components as compared to their conventional counterparts, and
5. identifying methods to establish the safety of new foods or food components when there are no conventional counterparts.

It is hoped that these and other international groups can both develop principals that are acceptable for new biotechnology products and help harmonize international regulations to facilitate international trade of biotechnology products. Preliminary FDA policy is consistent with the concept of substantial equivalence of new foods discussed in the OECD working papers and with the safety assessment procedures discussed in the FAO-WHO reports.

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Chapter 11

Scientific Issues in Food Safety

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

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Scientific Issues in Food Safety

In an ideal world, the food products we eat would contain no hazardous components and would be completely safe. We do not live in an ideal world. It is impossible to eliminate all potential food hazards, but food risks can be minimized by controlling microbial hazards, toxic constituents, and the nutritional value of foods. Scientists generally agree that when it comes to food safety, the number one concern is the problem of microbial contamination, followed closely by the effects of nutritional imbalance. The risks posed by toxic constituents such as pesticide residues, environmental contaminants, natural toxins, and chemical food additives, viewed as most important by the public, are generally considered by scientists to present lower risks (19, 28, 37).

It is impossible to precisely measure the number of foodborne illnesses that occur as a result of microbial contamination each year in the United States. Hundreds of thousands of cases are documented, including thousands of deaths. Due to underreporting, these documented cases represent only a fraction of the number of actual cases that occur. The Centers for Disease Control and the Food and Drug Administration (FDA) estimate that up to 33 million cases of foodborne illnesses occur annually, and some studies have placed the estimate as high as81 million (27, 55). This staggering number costs the U.S. economy billions of dollars in lost productivity each year. Some of the major genera of bacteria responsible for foodborne illnesses include *Salmonella, Shigella, Campylobacter, Listeria, Escherichia, Bacillus, Staphylococcus. Vibrio,* and *Clostridium* (botulism) (4).

The nutrient composition of foods affects their safety both directly and indirectly. Diets high in saturated fat, cholesterol, salt, sugar, and calories may be associated with an increased risk of cardiovascular disease and cancer. Failure to eat an appropriate diet indirectly may affect health by diminishing the body's capacity to prevent certain diseases such as cancer (17, 33). Additionally, the fad diets followed by many Americans can be dangerous.

Toxic constituents are either inherent to the food (produced naturally by plants and animals, particularly marine animals), result from microbial infections, or result from human activities such as environmental pollution or chemicals used in the production and processing of whole foods and food products. Public attention focuses primarily on toxins arising from human activities, and it is not surprising that the public views these constituents as posing the most severe risks. However, scientists generally feel that the levels of these constituents present in foods are generally low enough that the risks posed by them are less than those posed by microbial contamination, nutritional imbalances, and natural toxicants (19, 28, 37).

In part, this situation results from the extensive regulation of toxic constituents. Indeed, the food safety laws place heavy emphasis on the premarket approval of food additives and pesticide use. These laws also seek to minimize microbial contamination via extensive inspection of food establishments and sampling and laboratory analysis of foods for microbes. However, there are numerous ways in which a food may become contaminated, and it is an ongoing battle to try to minimize these occurrences.

The development of new technologies used to produce food products has raised new public concerns about food safety. This chapter will present some of the scientific issues pertinent to those concerns. The chapter will begin with a discussion of how conventional food products are assessed for safety. A discussion of issues raised by new food products produced with biotechnology will follow. The chapter will close with a discussion of the applicability of traditional safety assessment procedures to these new products.

FDA ASSESSMENT OF FOOD AND FEED ADDITIVES AND ANIMAL DRUGS

As discussed in chapter 10, FDA does not perform premarket evaluations on whole foods, only on food, feed, and color additives and new animal drugs. The FDA has the responsibility of assessing the safety of substances added to food and livestock feed and of drugs administered to animals used for human food. The FDA assesses the safety of food additives for human consumption and for quality control. Feed additives are evaluated for safety to the animal. Residue levels of feed additives or metabolizes related to the additive in edible animal products must be determined and assessed for their safety to humans. Animal drugs are treated in a similar manner to feed additives—they must be safe and effective for the animal, and any residues left in edible animal products must be safe for human consumption.

For products that might have an environmental impact (animal drugs in particular), an environmental impact assessment is also needed.

The basis for a safety assessment of additives and drug residues for humans relies on determining the toxicity of the additive or drug and the likely levels of human exposure to the substance. Human safety assessments require attention to the levels of toxic substances present. In 1564, the physician Paracelsus stated "Everything is poison. There is nothing without poison. Only the dose makes a thing not a poison. This concept of dosage still underlies toxicity assessments today.

Ingestion of excessive quantities of any substance, even one necessary for survival, can lead to death. Vitamin A is a necessary nutrient in small quantities, but is highly toxic in large quantities (24). Sometimes the acceptable consumption range is narrow as is the case with vitamin A. Therefore the dose is a fundamental determinant of toxic potential. The dose that a human is likely to consume will depend on the toxicity of the compound for the individual consuming the food, the level of the compound in food, and the levels of intake of the food. Exposure levels will vary by individual and by cultural, economic, and geographic factors. People have the ability to detoxify and/or excrete a large variety of potentially toxic compounds (10, 58, 59). However, in the elderly, children, and infirm those abilities may be compromised, raising their susceptibility to toxins in foods.

Firms seeking the approval of a food additive must submit a petition that contains information about the chemical identity of the substance, the anticipated level of consumption of the additive, and documentation of the efficacy of the additive for its intended use. Firms must also provide analytical methods to detect the additive and any related metabolizes that might result from use of the additive in food. Firms must also submit toxicity testing data.

Toxicological testing is conducted to ensure that the product is safe for its intended use and is required not only for the substance itself, but for any other substance that may form in and on food as a result of the use of the additive. Metabolic and pharmacokinetic studies are required to assess the fate of the test substance in the body. These studies help to identify metabolizes that might pose toxic risks.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Microbiologist checks growth medium **for visual evidence of harmful foodborne bacteria.**

The extent of testing required depends on the chemical structure of the ingredient, and on its intended level of use and consequent human exposure. Compounds whose chemical structures are such that they are unlikely to pose toxicological risks and those with low human exposure potential require only limited toxicological testing.

Full toxicological testing is required for high-use substances, especially when the chemical structure is judged not to lend itself to rapid and complete metabolism to innocuous end products. Full toxicological testing of food ingredients includes acute, subchronic, and long-term (including carcinogenicity) testing; impacts on reproduction; teratogenicity (ability to cause birth defects) testing; and genotoxicity (ability to mutate genetic material) testing. These tests are performed in multiple species.

Toxicology testing of additives is conducted by administering large doses of the test substance to an animal. The amount administered to animals is in increments so

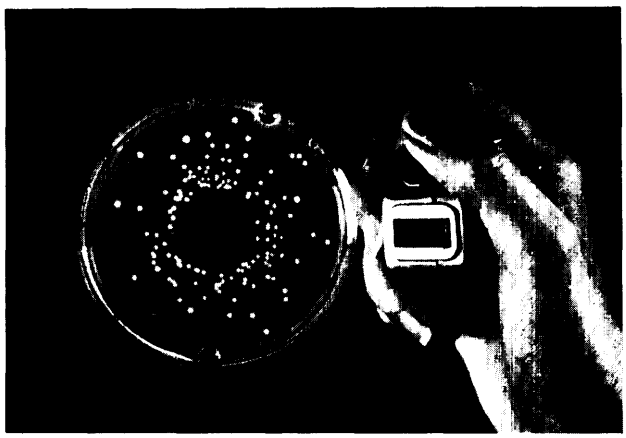


Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Fluorescent light illuminating colonies of bacteria in growth medium aids researchers in counting organisms present in studies that help ensure food safety.

that it can be determined what maximum daily dose can be administered without producing evidence of toxicity (i.e., the no observed effect level or NOEL). To be acceptable for inclusion in the diet of humans, food additives must have a margin of at least 100-fold between the highest estimated human exposure and the NOEL (20, 30).

If the product is intended for use in a food-producing animal, it must also be tested for human safety in a manner similar to food additives. The manufacturer must develop analytical methods to detect and measure feed additives, drug residues, and other potential metabolizes related to the additive or drug, in edible animal products. Residue levels are usually determined for muscle, liver, kidney, and fat, and where applicable, in skin, milk, and eggs (yolk and egg white). The length of time required for residues to be eliminated from animal products must also be determined (54).

The extent of testing required is tied to the degree of concern (anticipated hazard). This provides a flexible and scientifically valid procedure for assessing the safety of food ingredients, and allows for the safety evaluation of a wide range of food additives. It can be used to evaluate chemically synthesized or microbially derived additives, and drug residues resulting from medicated feeds or direct application to livestock. However, this method is not appropriate to evaluate the safety of whole foods, because toxicity is determined by feeding test animals large quantities of the ingredient. It is not possible to feed large quantities of whole foods needed to induce toxicity without so radically changing the metabolism of the test animal as to invalidate the results of the test. This constraint has not been a problem in the past, primarily because whole foods have traditionally been viewed as Generally Recognized as Safe (GRAS), and have not undergone formal toxicity testing. This situation may change with the development of new biotechnology products (20).

Quality Control

The FDA requires manufacturers to submit an extensive dossier of information pertaining to the method of manufacture of food or feed additives and of animal drugs. Detailed studies of the chemistry and purity of substances under the proposed conditions of manufacture, and information pertaining to their intended use is required. Petitions must include a description of the methods, facilities, and controls used to manufacture, process, and package the new product in sufficient detail to demonstrate that the methods will preserve the identity, strength, quality, and purity of the ingredient. Methods used in the synthesis, extraction, isolation, or purification must be described. Analytical procedures must be available that are capable of determining the active components with reasonable accuracy and of assuring the identity of such components, These procedures must have adequate sensitivity to determine the amount of the new ingredient in the final product.

Animal Safety Assessment

If the new product is a veterinary drug or feed additive used for livestock, the safety and efficacy of the product for the animal must be documented. Evidence must be provided that the drug or additive performs as claimed under the conditions of use specified in the petition. Animal drugs and feed additives must be tested for toxicity in all species of animals for which they will be used. Similar to food additives, the level of toxicity testing depends on the perceived risk of the substance. Drugs and additives may require acute, subacute, and chronic toxicity testing. Drug side effects must be evaluated. Reproductive effects may also be examined.

Environmental Assessment

The National Environmental Policy Act (NEPA) of 1969 requires Federal agencies to prepare a statement of the environmental impact of every major Federal action that significantly affects the quality of the human environment. Typically, the environmental review begins when industry submits a food additive petition, although FDA has the responsibility to evaluate any action within its jurisdiction that may significantly affect the environment.

Firms must either file for categorical exclusion from the requirements or submit an environmental assessment (EA).

Categorical exclusions include any actions under FDA authority that do not result in the production, distribution, or introduction of substances into the environment. Such actions might include inspection requests, changing labels, etc. Additionally, some additive and drug petitions seeking GRAS affirmation may also be excluded from the EA requirement. Examples would include products already marketed for the use for which the affirmation is sought and which are not toxic to organisms in the environment at expected levels of exposure (21 CFR 25.24(b)(7)).

Environmental assessments include, for example, data concerning the identification of the substances, physical containment procedures, waste stream treatment procedures, fate of the substance in the environment, and any special precautions taken to minimize release as a result of nonroutine or accidental situations. Information on traits that would limit survival, growth, or activity of organisms if released into the environment should be included. Verification of compliance with State and local requirements is needed (21 CFR 25.3 la). If the EA indicates that there might be adverse environmental impacts, then a full environmental impact statement may be required.

EPA ASSESSMENT OF RESIDUE TOLERANCES

The Environmental Protection Agency (EPA) has responsibility for determining the safety of pesticide residues in or on food for humans, or feed for domestic animals that are used for human food. Before a pesticide can be registered for use on a food or feed crop, either a tolerance or an exemption from the requirement of a tolerance must be established. A tolerance is the maximum level of pesticide residues that can be present in or on raw agricultural commodities, food, or feed transported in interstate commerce. Tolerances or exemptions from the requirement of a tolerance, must be established for each active and inert ingredient contained in the pesticide and for each raw commodity, processed commodity, and livestock species that might contain residues of the pesticide.

In a manner similar to FDA risk assessments of food additives, the EPA conducts a risk assessment to establish, or exempt from the requirement, a pesticide residue tolerance in food and feeds. This assessment includes identifying the existence and type of hazards that may be caused by pesticides; evaluating the relationship between the amount of the pesticide administered and the incidence of any adverse effects; and determining probable human exposure to the pesticide (53).

For pesticides used on raw agricultural commodities, [1] EPA tries to determine whether or not the pesticide can be used in such a manner that it is reasonably certain that no injuries will result in humans even after a lifetime of exposure. The risk assessment is based on the toxicology and residue data submitted by the petitioner.

Several kinds of data must be included when a petition is submitted for the establishment of a tolerance or exemption from a tolerance (21 U.S. C. 346a (d)). Required data include:

1. the name, chemical identity, and composition of the pesticide chemical;
2. the amount, frequency, and time of application of the pesticide chemical;
3. full reports of investigations made with respect to the safety of the pesticide chemical;
4. the results of tests on the amount of residue remaining, including a description of the analytical methods used;
5. practicable methods for removing residue in excess of any proposed tolerance;
6. proposed tolerances for the pesticide chemical if tolerances are proposed, and
7. reasonable grounds in support of the petition.

Petitioners also may be required to submit an analytical grade standard sample of the pesticide so that the adequacy of the residue detection method can be evaluated.

Residue chemistry data are designed to provide the information necessary to determine the site, nature, and magnitude of residues in or on food or feed. The purpose of the data is to identify what chemical residues are present and in what quantities. These data, along with information on use patterns of the pesticides, are used to determine dietary exposure levels. Information required includes qualitative data on the metabolism and degradation of the pesticide, quantitative data on the

[1] Raw agricultural commodities are considered to be fresh fruits, vegetables, grains, nuts, eggs, raw milk, and meats as opposed to foods that have been processed, fabricated, or manufactured by cooking, freezing, dehydrating. or milling among other processes (40 CFR180.1(e)).

magnitude of the residue in plant or animal tissues, and analytical methods to detect residues.

Residues present when a crop is harvested may not be identical to the applied pesticide. Environmental and host plant factors can degrade or metabolize an applied pesticide to form a variety of metabolizes. Plant metabolism data is collected to identify any types of pesticide residues that actually remain in agricultural crops as a result of these transformations. Field trials are conducted to determine the magnitude of the identified residues under conditions that simulate the way the pesticide will be used commercially. These data provide information about the kinds of residues likely to be present in raw agricultural commodities, as well as the amount of residues expected after pesticides are used in an approved manner.

Pesticide residues, degradation products, and metabolites all are tested for toxicity. Acute toxicity testing is required of all residues and provides information on the health hazards likely to arise from a single exposure to any toxic components associated with the pesticide. Changes in behavior, body weight, clinical symptoms, mortality, and tissue pathology among other symptoms are noted. Additional subchronic and chronic toxicity testing, oncogenicity testing, teratogenicity testing, neurotoxicity testing, and reproductive and fertility testing may be required depending on the pattern of *use* for the pesticide, its physical or chemical properties, the expected exposure of nontarget organisms, and the results of the acute toxicity testing.

As with FDA testing of pesticides, EPA toxicity testing involves feeding test animals large quantities of the pesticide to determine the dosage level at which the pesticide shows no observable or measurable effects in treated animals when compared to control animals (the no observed effect level, NOEL). Because of uncertainty in extrapolating data from test animals to humans, the NOEL is divided by a safety factor to determine the maximum levels considered safe for human consumption. The safety factor may vary depending on the type of data submitted and the chemical evaluated, with a factor of 100 the minimum generally used.

The EPA calculates a total amount of residues that a person can be exposed to in the daily diet. Based on residue data obtained from field testing, a petitioner may propose a safe tolerance level for humans. This proposed tolerance is multiplied by the number of commodities treated with the pesticide and the average consumption of the commodity by the general public. Similar exposure levels also may be calculated for specific groups that may be particularly sensitive to a pesticide, such as pregnant women and infants.

The EPA then compares the maximum level of residues considered safe with the total theoretical exposure level. If the maximum level considered safe is greater than the total theoretical exposure level, then usually the proposed tolerance level is established as the tolerance level of the pesticide in raw agricultural commodities. If, however, the maximum level considered safe is less than the total theoretical exposure level, EPA may reject the proposed tolerance level, or request further review.

With raw agricultural commodities, it maybe possible to establish a tolerance for pesticides that are carcinogenic. Additional risk assessments to determine the additional cancer risk will be conducted. Usually, if the additional cancer risk is less than 1 in a million, the proposed tolerance for the pesticide will be accepted.

Livestock feeding studies are required whenever residues result in or on crops used as feed items. Animal metabolic studies are conducted to determine the types and levels of residues present in edible animal tissues, such as meat, poultry, milk, or eggs.

Processing studies are required to determine whether residues in raw agricultural commodities can concentrate or degrade when those commodities are processed. If residues do not concentrate on processing, the tolerance established for the raw commodity applies to all processed food or feed derived from the commodity. If, however, residues concentrate on processing, a pesticide tolerance level must be established for the processed product (51).

Exemptions from the requirement of a tolerance can be granted if it appears that no hazard to public health will result from residues of a pesticide. Data that may be required to support an exemption include residue chemistry, product chemistry, and toxicology data, including subchronic toxicity, teratology, and mutagenicity studies.

Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA regulates microbial pesticides used in food and feed crops as well as chemical pesticides. To register a microbial pesticide, toxicity testing is required. Such testing might include acute oral, pulmonary, dermal, and intravenous administration. Additional subchronic and chronic toxicity testing may be required, as well as oncogenicity, mutagenicity, teratogenicity, and pathogenicity studies. The EPA has established protocols for such testing (57). Generally, however,

microbial pesticides have been exempted from the requirement of a tolerance.

POTENTIAL FOOD SAFETY CONSIDERATIONS INVOLVING BIOTECHNOLOGY-DERIVED FOODS

Currently, there is no evidence that whole foods, food or feed additives, animal drugs, or pesticides produced with biotechnology methods create greater food safety risks than these same products produced with traditional methods. However, biotechnology results in a new class of products, with which we have little experience. This lack of experience, combined with the novelty of the types of genes that can potentially be transferred, has raised concerns about the safety of such products.

Speculation about the potential food risks associated with biotechnology products has focused on the same general areas of concern as apply to traditional food products—namely, microbial contamination, nutritional imbalances, and presence of toxic constituents. The major new concern is whether or not the new technologies increase the potential for microbial contamination, whether or not they could lead to nutritional imbalances, and whether or not they might add new toxins or increase the levels of existing naturally occurring or synthetic toxins in food.

Potential To Affect Microbial Contamination of Foods

Several factors play a role in the growth of microbial organisms in food. Factors such as pH, type and concentration of acid, water activity, concentration of sodium chloride and other electrolytes, availability of nutrients and growth factors, and the levels of microbial growth inhibitors all function to inhibit or enhance the potential for microbial contamination and growth. Any change in the composition of a food that affects one or more of these factors will influence the chances of that food causing illness (37).

Products produced using biotechnology could potentially alter some of these factors in ways that could increase the potential for microbial contamination. For example, the development of low-acid fruits and vegetables might increase the possibility of botulism. Most tomatoes have a pH of 4.5 or lower, but some low-acid varieties are pH 5 or greater. When canned or processed, such low-acid foods are more likely to support the growth and toxin production of *Clostridium botulinum* than are high-acid varieties.

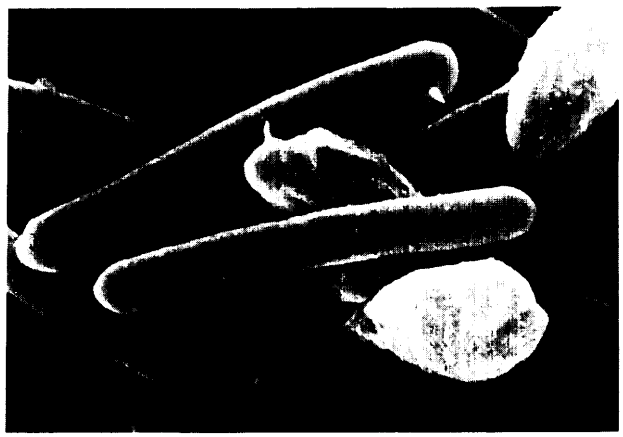


Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Clostridium botulinum is a toxin-producing food spoilage organism and dangerous human pathogen. The sac-like dormant spores can survive conditions that are lethal for the rod-shaped bacterial cells. Magnification is about 8,500 times.

Removal of substances that act as microbial growth inhibitors may also increase the potential for contamination. For example, there is some evidence that caffeine in coffee beans may suppress aflatoxin production (3 1). Suppression of caffeine production in coffee beans could increase the potential for contamination. It may also be possible to introduce nutrients into foods previously lacking in sustenance. If the introduced nutrient is a required growth factor for a particular microbe, its introduction might enhance the potential for infection by the microbe.

Changes in factors that affect microbial growth might also be in the direction that inhibits the growth of pathogens. For example, delayed softening of tomatoes may decrease the potential for mold and bacterial growth. Nor is the potential for such events to occur limited to foods produced with biotechnology. Low-acid tomatoes produced with traditional methods are currently being marketed. But new technologies do warrant an awareness of the potential to enhance microbial contamination.

Potential To Affect Nutritional Content of Foods

Whole foods are compositionally highly complex. They contain carbohydrates (e. g., starches, sugars, gums, cellulose, etc.), fats, proteins, minerals, vitamins, enzymes, genetic materials (e.g., DNA, RNA), waxes, plant pig-

ments, essential (volatile) oils (e.g., peppermint and citrus oils), alkaloids, and many other compounds. The levels and types of these constituents present vary significantly between species due to different genetic composition, but even within the same species, or even variety, the levels can vary substantially as result of different environmental factors. Different soil types, sunlight, rainfall, temperature, and agricultural practices such as irrigation, planting date, maturity at harvest, and storage conditions substantially can alter the level of food constituents present (20).

Information is available concerning the normal levels of major nutrients in several food products. In general, levels of nutrients vary by two- to three-fold in foods, although higher levels of variation are seen. For example, the level of beta-carotene (a precursor of Vitamin A) in carrots ranges from O to 370mg per 100 grams of tissue (42). In general, such nutrient variation does not pose severe problems for humans, because humans eat a wide range of food products, even in situations where there is heavy dependence on one source of food for most of the calories in the diet. Thus, diet quality is measured by the sum total of everything eaten, and is not generally based on a single crop or product. Decreases in the nutritional value of one crop may not be significant unless that one product is the major or only source of that nutrient for the population. Likewise, increases in a nutrient compound may not be significant unless the population eats large quantities of the food containing the compound and/or the compound has a narrow range of toxicity acceptability (35).

Because of the diversity of food products available in the United States, alternative sources of major nutrients are available. However, some foods do constitute the major source of particular nutrients. For example, Americans rely on milk and milk products as the major food source of calcium, on oranges and orange juice to provide most of the vitamin C consumed, and on carrots to provide the precursors of vitamin A. Furthermore, some nutrients (e. g., vitamins and minerals) can be toxic in high levels, and a significant increase could potentially pose some risks. Thus, an evaluation of the levels of nutrients in individual food types and the amount of the different food types eaten will determine if there is likely to be a nutritional impact.

Nutritional impact depends not only on the amount of the nutrient present in the food, but also on how much of the food is consumed by an individual, and the individuals physiological state. If technological changes significantly alter the types or amounts of foods eaten, nutritional risks could result from this changed behavior. For example, technological changes that alter the growing season or geographical region where foods are grown could alter the seasonal or quantitative availability of some foods such that consumers may eat more or less of that particular food. Technology could change the quality of the food (e. g., decreased fat in meats, altered taste of the food) such that consumption patterns would change. Uncertainty about technologies used to produce some foods may cause some consumers to avoid that food. For example, surveys have indicated that if bovine somatotropin (bST) is used to produce milk, some consumers will decrease their consumption of milk and milk products, potentially with a consequent reduction in calcium consumption. Thus, use of technologies that result in significant changes in consumption patterns may also create nutritional risks.

Whereas some biotechnology research is conducted for the purpose of altering the nutritional composition of foods (i.e., efforts to decrease the fat content in meat products and to increase lysine in corn), potential may also exist to inadvertently alter a critical nutrient biosynthetic pathway. If an important nutrient like vitamin C was inadvertently reduced in oranges, this potentially could have significant nutritional implications. Some nutrients are needed in small quantities but are toxic in large quantities. Increases in the levels of these nutrients could be significant from a food safety standpoint. Nutrient levels in normal foods differ significantly. Additionally, changes in acidity or solidity, for example, may alter the ability of food constituents to be utilized as nutrients. Similar to the development of new varieties using traditional breeding practices, which can also alter the level of important nutrients, careful attention should be paid to whether there are significant changes in the level of important nutrients between a biotechnology-derived food and its traditional counterpart, or whether the change is within the normal range of nutrient variation for foods.

Potential To Affect Toxic Constituents of Foods

In addition to the potential impacts of biotechnology on microbial contamination and nutrient composition of foods, there is concern that new biotechnology-derived food products may have new and/or increased levels of toxic compounds. Postulated mechanisms for this increased toxicity include:

1. the transferred gene(s) code for toxic compounds,
2. the transferred gene stimulates the production of secondary compound(s) that are toxic,
3. the marker genes used for identification of transformed cells code for toxic compounds,
4. the production of naturally occurring toxins increases unexpectedly as a result of the undirected insertion of the transferred gene into the host genome (the so-called pleiotropic effects), or
5. plants unexpectedly accumulate environmental toxins (e.g., heavy metals) in edible tissues (likely only to be a problem for plants developed to grow in contaminated soils) (16, 20, 30, 44).

When transferring genes into host organisms, a genetic construct consisting of the gene to be transferred, marker sequences to identify those organisms that have been genetically transformed, and regulatory elements such as promotors and enhancers that control the operation of the transformed gene are all inserted into the new organism. Additionally, in many transformations, vectors are used to insert the gene construct, and it is possible that some of the vector DNA could also be inserted into the host organism. Some groups have expressed concerns that the expression products coded for by these genes may be toxic.

Primary and Secondary Gene Products

When a gene is transferred into a host organism it produces a gene product (protein). This gene product may be the final active product, or it may act as an enzyme or hormone that mediates the production of other compounds. Gene products may therefore have direct, primary effects and indirect, secondary, or compensatory effects. Most proteins are generally nontoxic, and no known proteins exhibit mutagenesis or carcinogenesis. A few highly specialized proteins (i.e., cytotoxins, enterotoxins, and neurotoxins) are acutely toxic, but these proteins are generally well characterized as to their source and mode of action. Proteins, unlike some chemicals, are constantly being degraded in an organism and do not accumulate in tissues (21, 22).

Most proteins are readily degraded during digestion but a few do not. These exceptions are characterized by fairly well-understood chemical interactions that stabilize parts of the protein molecules, thereby enabling them to survive digestion partially intact. Most of these protein fragments are excreted in the feces, but some enter the blood stream where they may elicit immunological reactions. Allergic reactions have been documented to protein products found in many common foods including nuts, peanuts, chocolate, barley, rice, wheat, citrus, melons, bananas, tomatoes, spinach, corn, potatoes, and soybeans. In some cases, the immunological agent is known to be a protein, while in other cases a glycoprotein (a compound containing both a carbohydrate and a protein) is involved. With glycoproteins, it is not known whether it is the protein portion or the carbohydrate portion that is causing the immune response. Both components could be affected by genetic modification (21, 22).

In cases where a gene product mediates another chemical reaction, indirect effects from gene transfers may occur. For example, the primary gene product might be an enzyme that catalyzes production of another product. Alternatively, the gene product might be a protein hormone that itself produces biological effects as well as stimulates production of other compounds that have biological functions. As an example, somatotropins (growth hormones) are protein hormones that elicit several physiological responses in the body, such as enhancing protein accretion in immature animals. Somatotropins also stimulate the production of other compounds such as insulin-like growth factors (IGFs), which also elicit physiological responses. Thus, in this example, the primary gene product would be somatotropin and the secondary gene product would be IGF.

Unlike the primary gene expression product which is a protein, secondary products do not necessarily have to be proteins. Enzymes can catalyze the production of other proteins or the production of other classes of chemicals such as carbohydrates, fats, etc. Protein hormones may also stimulate the production and release of steroidal hormones. Concern has been expressed that these nonprotein secondary metabolizes may be chemically more stable, may accumulate in body tissues (most notably fat) and may be easier to absorb through the digestive system than protein products. Thus, indirect effects of gene transfer may be an important food safety consideration if the organism compensates for, or responds to, the primary gene product by producing increased levels of a compound that displays oral toxicity (22). Food safety evaluations must include an assessment of both primary and secondary products.

Marker Genes

Various marker genes, including antibiotic resistance genes, are used in biotechnology as a means of distinguishing between cells that have been genetically transformed and those that have not—only the transformed cells will contain the resistance gene. Many first-generation transgenic plants use as a marker the gene for

neomycin phosphotransferase, an enzyme that converts the antibiotic kanamycin to an inactive form. Some groups have expressed concern over the inclusion of such marker genes in genetic constructs. Possession of a particular antibiotic resistance gene allows an organism to grow in the presence of normally toxic levels of the particular antibiotic the enzyme deactivates. Thus, the organism is resistant to that antibiotic.

The primary issues raised with respect to the use of antibiotic resistance genes as markers are not those of toxicity per se. Rather, the issues focus on whether or not potential exists for the transfer of antibiotic resistance from food products to intestinal bacteria during digestion (thus creating a strain of intestinal bacteria resistant to kanamycin) and whether the presence of these genes will interfere with therapeutic antibiotic administration.

Evidence to date does not suggest that naturally occurring antibiotic resistant organisms transfer resistance in the intestinal environment. Usually DNA rapidly degrades in the presence of acids and enzymes contained in the gastro-intestinal tract, significantly decreasing the likelihood of an intact gene being transferred. Additionally, the promoter sequences used with the kanamycin resistant gene are plant promotors rather than bacterial promotors; plant promotors do not function in bacteria so there is some question as to whether the gene would be active even if transferred. Additionally, kanamycin resistance is relatively common among soil microorganisms, and thus it is likely that humans are already consuming the gene. The likelihood of the transfer of kanamycin resistance seems remote.

A more pertinent concern with respect to the use of antibiotic resistance markers is the possibility that they could interfere with therapeutic antibiotic administration if the food containing the resistance enzyme is ingested with antibiotic administration. This may not be significant for kanamycin, but the issue must be addressed. The FDA has been petitioned for an advisory opinion concerning the use of the kanamycin resistance marker in transgenic plants. To date, FDA has not issued that opinion.

In addition to the kanamycin resistant marker, other marker genes can and are being used. Such genes include those that code for herbicide tolerance and the lacZY color marker. Concerns have been expressed that these markers might also create novel gene products or associated secondary metabolizes. Once again, the expression products and the genes coding for these markers are well characterized and have been studied for many years, so it seems unlikely that they would cause safety problems.

In general, the marker genes currently used code for gene products that are well characterized and have been part of the food system for many years. Use of such markers significantly reduces the potential for food safety problems. Additionally, new research showing that these genes can be successfully removed from transgenic crops may eliminate many of the concerns associated with the use of marker genes.

Vector Material

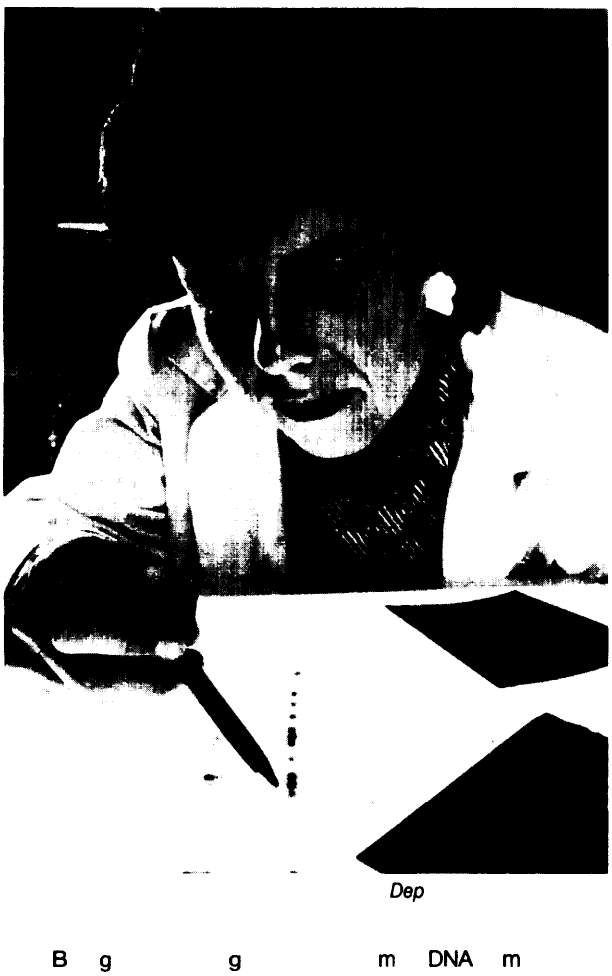
Viral or bacterial plasmid vectors are sometimes used to transfer genes from one organism to another. Some groups have expressed concern that these vector sequences may code for toxic substances. The likelihood of this occurring is significantly decreased by using vectors derived from microbes that do not produce toxic substances or that are not closely related to microbes that produce toxic substances. Additionally, use of plasmids from bacteria that have a long history of use in food products decreases the likelihood that the vector used will code for toxic substances. It is a commonly accepted practice to use vectors with these characteristics in genetic engineering (e. g., the Ti plasmid of Agrobacterium tumefaciens). Thus, the probability of vector toxin production is low.

Unexpected Pleiotropic Effects

A primary concern raised with respect to biotechnology products is the potential for pleiotropic effects. Pleiotropic effects are secondary changes in metabolism (i.e., phenotypic alterations) that result from a single genetic change (50). Genetic material contained in cells is composed of sequences of DNA that code for gene product (the coding regions), sequences of DNA involved in controlling gene expression (regulatory sequences), and sequences of DNA for which there is no readily apparent function (the noncoding regions). The majority of the plant genome consists of this noncoding DNA.

As discussed in chapter 2, when genes are introduced into a plant, there is little control over where the gene is inserted. The new gene can be inserted into the coding regions of a host gene, into the noncoding regions of a host gene, or within regulatory regions of a host gene. This undirected insertion of the gene raises the possibility that

- the site of insertion will affect the level of expression of the introduced gene itself,
- the site of the insertion is such that host organism genes will be activated or inactivated, or



. the site of insertion will be such that there will be no inadvertent effects on the host organism (20).

Gene expression levels (i.e., the amount of gene product actually produced) vary depending on a number of factors, including the number of copies of the gene incorporated into the host and the position of the gene within the host genome. The mechanism by which insertion site affects expression levels is not fully understood; however, the insertion site and expression levels are passed on to the offspring in a consistent manner (20, 41). Expression levels of the gene may be too high or too low or absent altogether. Depending on the nature of the gene, overexpression may be detrimental to the host organism itself, or pose food safety risks for human consumption. Underexpression, and particularly no expression, may pose no technical safety issues, but may still raise concerns among a public uncertain about the process of biotechnology itself. This situation has arisen with transgenic animals in which the gene was incorporated into the host genome, but not expressed. Some consumer groups have opposed the slaughter of these experimental animals. The Food Safety and Inspection Service (FSIS) is in the process of formulating guidelines for the slaughter of these types of animals.

Insertion of the foreign gene into noncoding regions of the host DNA may cause no disruption of any of the host genes. These regions do not code for gene expression products, so disruption of these sequences is unlikely to result in the activation or inactivation of host genes. The more likely consequence would be production of the expression product of the inserted gene itself, rather than any unexpected pleiotropic effects (20, 21).

The third, and likely most significant possible pleiotropic effect of gene transfer, involves the activation or inactivation of *host* organism genes as a result of undirected insertion of the foreign gene. The foreign gene may insert into the coding sequences of a host organism gene or into the regulatory sequences of a host organism gene.

Insertion of foreign genetic material into a regulatory sequence of the host organism could destroy the ability of the regulatory sequence to control the expression of host organism gene(s). The foreign gene construct that is inserted into the regulatory sequence of the host gene, moreover, contains a regulatory sequence itself, which could affect the expression of the host gene(s). The foreign regulatory sequence may be activated under different circumstances than the host organism's regulatory sequence, thus altering the expression of the host organism genes in terms of amount, timing, and/or tissue location. The significance of this occurrence may, in part, be influenced by whether or not the promotor sequence used is inducible (controlled by specific stimuli) or constitutive (turned on all the time) (20, 21, 56).

If the foreign gene is inserted into the coding region of a host gene, then the most likely outcome would be the inactivation of the host gene. This is because the foreign gene must be inserted in the proper place and in the proper direction (i. e., the sense direction) for activation to occur. Insertion into improper sites (even if in the proper direction) or in the backwards direction (i.e., the antisense direction) will cause the gene to be deactivated. The probability that the foreign gene will be inserted in the improper position or wrong direction is higher than the probability that the gene will be inserted into the proper position and direction (20).

Host gene inactivation could present food safety risks if, for example, it led to decreased levels of nutritional

components. Inactivation of enzymes or hormones that play key roles in biosynthetic pathways could lead to the use of alternate pathways and the potential buildup of some secondary metabolizes.

If the insertion of foreign genetic material is such that host organism genes are activated (i.e., the insertion is in the regulatory rather than coding region), several possible outcomes could result, some of which could pose food safety risks. Activation of host genes could result in increased levels of naturally occurring toxins or the appearance of those toxins in plant tissues where they do not normally appear. For example, a toxin normally produced only in the leaves of a plant now may be produced in the seeds as well. Other possibilities include the increased uptake and concentration of environmental contaminants by the organism (6, 11, 14, 23, 30, 32, 36). It is more probable that foreign gene insertion will lead to host gene deactivation rather than activation, although the probability of host gene activation is not zero.

Ten times more DNA is contained in the coding regions of genes than in the regulatory regions. Therefore, if gene insertion is truly random, gene inactivation by insertion into a coding region of a gene is about 10 times more likely to occur than gene activation by insertion into a regulatory region of a gene. However, it is possible that gene insertion may occur preferentially in selected areas of the genome (e. g., in active genes) rather than in a completely random fashion. If this is the case, host gene activation might occur with a higher probability.

The potential activation of genes that code for natural toxins in the organism is of particular concern. Plants are known to contain hundreds of toxic compounds, and it is likely that they contain many more that have not been identified. For example, roasted coffee is known to contain at least 826 volatile compounds that could potentially have toxic effects (1). At least 148 naturally occurring food compounds have been demonstrated to have acutely toxic effects in experimental animals, livestock, or humans when consumed.

In humans, most of the toxic effects of food have occurred as a result of abnormal diets or substance abuse, but at least 14 food compounds can be acutely toxic under certain circumstances even when consumed in quantities within the range of normal dietary intake (table 1 l-l). For example, the solanine content of white table potatoes normally ranges from 2 to 20 mg/10Og of tissue, but abnormal weather conditions can raise the concentration. Just 100 mg of solanine is enough to evoke death in some individuals. Low cyanogen varieties of cassava, if improperly prepared, are capable of yielding 20 to 40 mg of hydrogen cyanide per kilogram of cassava. However, some varieties of cassava can yield 20 times that much hydrogen cyanide, which is enough to be deadly. Increased levels of these known naturally occurring toxins as a result of biotechnology would certainly present food safety risks (20, 23, 26, 30, 32, 60).

Table n-l-Naturally Occurring Toxins in Foods That Have Been Documented To Have Acutely Toxic Effects on Humans Consuming Normal Diets

Toxic compound	Food source
Acetylandromedol	Honey
Andromedol	Honey
Anhydroandromedol	Honey
Desacetylpieristoxin	Honey
Gelsamine	Honey
Tutin	Honey
Hyenanchin	Honey
Cicutoxin	Milk (19th century America from water hemlock)
Hypoglycin A	Ackee fruit
Linamarin	Lima beans and Cassava
Lotaustralin	Lima beans and Cassava
Solanine	Potatoes
Curcurbitacin E	Squash, Cucumber
Nitrates	Spinach, and other green leafy vegetables

SOURCE: International Food Biotechnology Council, 1990.

Sufficient knowledge has accumulated regarding naturally occurring acutely toxic plant toxins to provide assurance that the food supply contains either safe levels of these toxins or can be processed in a way that minimizes or eliminates their acute health effects. However, much less is known regarding the role in chronic disease of naturally occurring plant toxins currently consumed (30). A large number of naturally occurring compounds frequently found in foods appear to be mutagens and possible carcinogens. For example, of the 826 volatile compounds contained in coffee, only 21 have been tested for chronic effects, and 16 of them were found to be carcinogenic in rodents (1, 2, 3). Potentially, the number of such substances could reach into the thousands, we know neither their identities, their normal concentrations, nor their long-term impacts on human health (1, 2, 3, 20).

Compared to plants, substantial literature on microorganisms and their toxins relative to foodborne illness exists. Considerable information concerning the genetic and/or environmental determinants of microbial toxin expression is also available. This information could be used to structure strategies for determining the safety of microbially derived food products (7, 20, 30, 38). The microbial toxins of primary concern are those that are

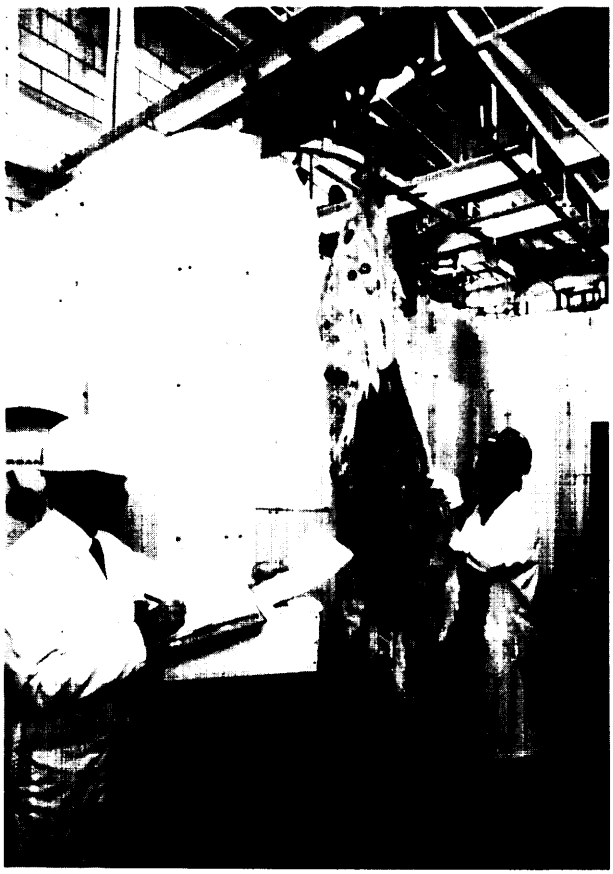


Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Microbiologist obtains samples for microbial analysis from carcass, Production of toxins by animals consumed for food purposes is rare.

active orally and are known to be produced by organisms related to those used in food processing.

The production of toxins by animals consumed for food purposes is rare and is generally limited to a few marine species such as the puffer-fish (6, 23, 32). Severe insertional effects are likely to be uncommon because such impacts would probably lead to the death of the embryo. Insertional effects could potentially affect the manner in which an environmental toxin is detoxified, or could increase the accumulation of contaminants such as heavy metals, pesticides, or orally active compounds in edible tissues. A significant change in the accumulation of such compounds is likely to be detrimental to the animal itself; thus, the health of the animal serves as a preliminary screen for toxic effects (5).

Plietotropic effects might also result from using tissue-culture techniques to regenerate genetically transformed cells. When the genetic material is transferred into a cell, the cell must first be regenerated into a whole plant using tissue-culture techniques before additional breeding can occur. Plants regenerated from cell tissue culture have sometimes shown striking differences among themselves and from the parent cells from which they were regenerated. The process of separating mature plants cells and regenerating those cells into whole plants releases a pool of genetic diversity inherent in the plant. This process is referred to as somaclonal variation, and it is being used in traditional breeding programs to identify new traits that might be of agricultural interest. Because transgenic cells are regenerated into whole plants, it is possible that some unexpected gene products might be expressed in the mature plant. Frequently, the gene expression of these somaclonal variants is not stable, and they are not inherited by subsequent generations, but this does not hold in all cases (34).

For whole foods that rely almost exclusively on the use of tissue culturing in the breeding program, these effects might be significant. For many transgenic plants (i.e., grain crops), however, they may not be. Transgenic crops will not immediately go from the laboratory to the dinner table. In some cases, backcrossing with traditionally bred lines may be needed. Even if the gene is transferred to a well-adapted parent line, the stability of the gene and the agronomic performance will need to be determined. Thus, if a key enzyme is deactivated, an essential pathway disrupted, or detrimental somaclonal variants occur, it is likely that the crop will not perform well in field trials and will be screened out and never commercialized. Likewise, as a result of the Lenape incident, screening has improved for compounds known to be acutely toxic to humans if consumed in high enough quantities. While these methods do not guarantee that all unexpected and undesirable effects will be detected prior to commercial release, it is likely that many of the more significant ones will be.

Unexpected results can and do happen frequently as a result of traditional breeding. This situation is not unique to biotechnology. Indeed, many of the issues raised today concerning biotechnology are the same concerns raised in the 1970s with respect to the development of new crop varieties by traditional breeding and the use of chemicals and irradiation to mutate microorganisms. The majority of these unexpected effects that occur have not been demonstrated to cause severe food safety risks, although on rare occasions there are exceptions. Unexpectedly high levels of toxic compounds have occurred as a result of traditional breeding. The classic example is the development of a new potato variety (Lenape) in the 1970s.

This new variety had better processing characteristics and enhanced disease resistance over traditional varieties. It also had significantly elevated levels of solanine, which were fortunately discovered before any illnesses resulted (20, 30, 61). However, this example involves a crop that contains a known, acutely toxic compound. Most crops do not have such compounds. Therefore, even if unexpected effects do occur as a result of biotechnology, they may not present significant food safety risks just as they do not when they occur during traditional breeding. Clearly, particular attention should be paid to those crops known to produce highly toxic compounds.

APPLICABILITY OF CURRENT SAFETY ASSESSMENT METHODOLOGIES TO THE PRODUCTS OF BIOTECHNOLOGY

The FDA does not routinely review for the safety or toxicity of food, only for food additives. Food additives generally are synthetically produced in batch quantities and added to foods. Because of the way these compounds are produced, a safety assessment approach has been established that administers large quantities of the additive to animals to determine at what level any toxic effects may occur. Concentrations of additives must be well below the level at which any toxic effects may have occurred. This type of approach will be difficult to apply to genetically modified whole foods.

Whole foods are complex mixtures of chemicals, not single chemicals. It is not possible to feed whole foods in quantities sufficient for toxicity assays without simultaneously producing gross disturbances in the nutrient balance and physiology of the test animal, which invalidates the results of the test. Experiments involving whole foods fed at the levels approximating the intended use for humans lack the sensitivity to detect anything but the most potent toxins. Thus, conventional procedures of toxicological investigation lack the sensitivity necessary to ensure the safety of genetically modified whole foods under chronic use conditions. It is for these reasons that the safety evaluation of genetically modified whole foods requires that innovative new approaches be developed.

Many first-generation transgenic crops involve the transfer of a single gene, often derived from a different species than the host (transformed) plant. The foreign gene may or may not significantly alter inherent biosynthetic pathways in the transformed plant. In the future, however, genetically engineered crops will likely be more sophisticated. Multiple genes will be transferred. Host plant biosynthetic pathways may be significantly altered such that the levels of several naturally occurring compounds in the transformed plant will be altered.

Recently, for example, it was announced that the first protein plant hormone has been identified (13). This hormone mediates several metabolic reactions within the plant. Research is being conducted to identify additional plant protein hormones and to possibly clone and transfer the genes that code for these hormones. Thus, future transgenic plants may display significant compositional differences from those available today. Current safety assessment methods that rely on testing individual components will be increasingly inadequate as a method to assess the safety of these more complex genetically engineered plants.

Finally, as discussed above, the potential food safety risks that may result from the use of biotechnology in food production fit two general categories—those that can be anticipated based on the structure and known metabolic activity of the gene product, and unexpected results, such as the enhanced production of naturally occurring toxic substances, that might result from the undirected insertion of the gene.

For all these reasons, a new approach to safety evaluations is needed in the era of biotechnology. The new approach has two key elements:

1. knowledge of the genetic modification practices used and the inferences this has for product safety, and
2. compositional studies designed to evaluate whether changes in composition of food products might lead to safety concerns under the intended conditions of use (30).

Understanding the genetic modification practices used and the inferences this has for product safety provides information concerning the types and nature of gene products likely to be present. Compositional studies yield information on any unexpected effects that may occur as a result of the genetic modification. Since the effects are unexpected, one does not know what kinds of gene products to evaluate for toxicity. The way to obtain this information is to compare the transgenic organism to its conventional counterpart and note any significant changes in the amounts of common constituents associated with the foodstuff and for identifying any new constituents that may have been introduced by the genetic modification process (30). Knowing what these changes are

provides a basis on which to conduct a safety evaluation of the new food product.

Knowledge of the Genetic Modification and Inferences

An analysis of the safety of the gene products will require understanding the type and nature of products expressed, any toxic effects of these products, and the levels at which they occur in the food. These are the same issues that must be addressed when evaluating the safety of conventional food additives. As with the safety assessment of traditional food additives, the assessment of biotechnology-derived foods must begin with the identification of the types and nature of gene products present. Such information can be obtained by evaluating the genetic construct itself and understanding the metabolism of the product of the inserted gene.

Evaluating the genetic construct itself includes analyzing both the product of the newly transferred gene and the products of any other genetic material transferred with the desired gene (e. g., marker sequences, regulatory sequences, vector sequences). The information needed to evaluate the genetic construct includes:

- the physical size, structure, and functional limits of the coding region;
- the physical extent and functional properties of the regulatory DNA regions (e. g., where the regulatory sequence occurs relative to the coding sequence, the relative strength of the regulatory sequence;
- the starting signal for transcription of the gene); and
- the structure and function of the marker sequences (20).

This information is needed whether the host organism is a microorganism, a plant, or an animal. In some cases, this information is already available in the public literature, but if it is not, it usually becomes available as a result of the genetic engineering process itself, or it can be obtained relatively easily with genetic engineering techniques.

An understanding of how the inserted gene functions in the plant is also needed. An ideal situation is to have stable and predictable gene expression. Information useful in determining gene expression in the plant includes an estimate of the number of gene copies inserted, whether they are inserted into the chromosomes or other organelles that contain genetic material (i.e., the mitochondria or chloroplasts), and whether gene expression is inducible or constitutive (turned on all the time). Tissue location (plant part) and concentration of gene expression products during the plant's life cycle should be determined. And any evidence of the gene moving to other locations within the genetic material should be evaluated (56).

The mode of action of the gene product also should be assessed. In general, with food additives and pesticides, these compounds and any degradation products are traced in the plant by radioactively labeling the compounds. Such an approach may not be adequate to identify metabolic products inherently produced in a plant as a result of genetic engineering. New analytical methods and greater understanding of basic plant metabolism will be needed to identify endogenous plant metabolizes that result from genetic engineering.

Once the gene products have been characterized, their potential to produce toxic effects must be addressed. The material used for the toxicity testing should represent as closely as possible the expression product as it actually occurs in the plant. It is preferable to develop methods that could assess the toxicity of the whole food, i.e., the form in which it is eaten. However, such methodology is not currently available. An alternative approach is to isolate and purify the gene product from the plant in sufficient quantities to conduct traditional toxicity testing (i.e., administering large doses of the substance to a test animal). Isolating sufficient quantities of primary and secondary gene products from whole foods, however, may be difficult in some cases. The gene product must be extracted from the food. In some cases, methodology for such extraction may not be available, and new analytical techniques will need to be developed.

If the gene product does not undergo significant post-translational modifications in the plant, an alternative approach to obtaining sufficient quantities of the gene product for toxicity testing might be to produce and purify the product from a microbial system. Even if post-translation modifications occur, knowledge of the sequence of the gene allows for the use of computer algorithms to identify other proteins with related sequences, taking into account any post-translational processing that might occur to alter the protein. Once the protein family has been identified, it may be possible to establish a history of safe consumption of closely related proteins in other foods. This does not guarantee the safety of any specific protein, but each new case does not have to be treated as being entirely novel; the relationship of a protein to other proteins with a similar function provides additional information that can sharpen the focus of the safety evaluation (5).

Box II-A—FDA Safety Review of a Food Enzyme Derived From a Genetically Modified Bacterium

Rennet, an enzyme preparation isolated from the forestomach of calves is used to clot milk in the cheesemaking process. The principal enzyme contained in rennet is chymosin. The FDA affirmed rennet as GRAS for use in food in 1983. However, this source of the chymosin enzyme is expensive for food processors, and an appropriate substitute would be beneficial to the industry.

In February 1988, Pfizer Central Research (Pfizer Co.) petitioned FDA to affirm as GRAS, a chymosin preparation obtained from genetically inserting a chymosin gene into a bacterium. This genetically modified bacterium was then used to bacterially ferment large quantities of chymosin, which could be used in place of rennet. Chymosin **was the** first biotechnology-derived food additive reviewed by FDA.

During the review, FDA viewed the chymosisn preparation as a product consisting of an active enzyme plus any impurities that may have been introduced during fermentation and processing. The FDA was interested in determining whether the cloned chymosin gene yielded a protein enzyme of the same structure and function as is contained in rennet.

The cloned gene was sequenced and other analytical tests performed to establish the chemical identity of the resulting enzyme. This cloned chymosin enzyme was tested to determine if it had the same functional activity as chymosin derived from rennet; its ability to clot milk was tested under various conditions of temperature, salt concentration, and PH. This information was used to determine that the cloned chymosin enzyme was indistinguishable from that contained in rennet. The safety of the chymosin enzyme preparation was also tested by feeding large quantities of the preparation to laboratory animals. No adverse effects were detected.

The FDA also examined the safety of the bacterium into which the chymosin gene was inserted. The bacterial strain used has been used widely as a laboratory organism for at least 30 years without any reported incidents of illness. The strain does not colonize the gut of man or animals, even when present in high concentrations; does not produce toxins; and lacks the characteristics necessary for pathogenicity. Additionally, the process used to purify the enzyme destroys the bacteria and removes most of the microbial material from the final product. Because the bacterial strain used contained an antibiotic resistance gene as a marker, FDA also sought to ensure that this gene was destroyed during purification and that there was no possibility of the gene being transferred to bacteria contained in the human gut.

Chemicals used in the purification process were also **evaluated** to determine if they presented safety concerns. Compounds used in processing were those already approved as food additives or were GRAS. The resulting chymosin preparation was considerably purer than the rennet preparation currently in use.

After review of test data and published literature pertinent to the use of chymosin in food, FDA affirmed the GRAS status of biotechnology-derived chymosin in March 1990.

SOURCES: Federal Register, vol. 55, No. 57, Mar. 23, 1990, pp. 10932-10936. Eric L. Flamm, "How FDA Approved Chymosin: A Case History," Bio/Technology, vol. 9, April 1991, pp. 349-351.

For microorganisms used as a source of simple chemical additives, the safety assessment includes identifying: the host organism, any evidence of pathogenicity or toxin production, the function of the inserted gene, and the identity of any organisms that contributed genetic material to the final construct. In addition, characterization of the inserted genetic material is needed to ensure the absence of sequences that may encode harmful substances. Insertional and genomic stability, chemical specifications, dietary use and exposure, and other relevant information must also be evaluated. Safety evaluation of the insert itself focuses on its expression product. In addition, the fermentation process is evaluated for variation and control elements. The purity and identity of the final product should be maintained throughout the production process. This approach was taken with the FDA review of chymosin, the first chemical additive produced by genetically modified bacteria to be approved (box 1 l-A).

In keeping with the approach that chemicals with the highest potential risks must undergo the most extensive toxicity testing, the use of genetic elements that have a safe history of use in food could require a less rigorous evaluation than is necessary if genetic elements foreign to the food supply are used. "Safe" genetic elements

might consist of genetic material from nonpathogenic, nontoxigenic microorganisms that are commonly associated with or found in foods; and genetic elements, characterized or uncharacterized, used as source material for the genetic modification of food species via conventional breeding procedures (20).

Assessment of Potential Unexpected Effects

While some of the traditional safety assessment practices may be used to identify the toxicity of primary and secondary gene products, the evaluation of the potential impacts of gene insertion effects will require a different approach. The major difficulty encountered is documenting the effects of undirected insertion since one does not know what compounds could be produced or what expression levels could be enhanced.

The way to determine whether unexpected expression products or nutritional deficiencies have in fact occurred, is to compare the compositional changes of a genetically modified organism with that of a traditional organism, or a selected reference organism. Bacteria commonly used in food production are generally well characterized, and the possibility of production of toxic compounds is very low if the host bacterium does not normally produce toxins. Demonstration of unexpected results in more complex organisms, such as plants, will be complicated by the large size of the genome and the fact that toxic products may only be produced under special conditions (38).

To compare transgenic plants to traditional or reference plants requires knowing the normal range of the latter's nutritional components, and identifying any naturally occurring toxic compounds that have significantly increased levels in genetically modified plants. The inadequacy of the information concerning whole food composition of traditional foods limits the ability to make such comparisons at the present time (30).

While knowledge concerning the normal range of toxic compounds in raw foods is limited, even less is known about the normal range of such toxins in processed foods. While food processing and cooking often lowers the levels of toxic factors, sometimes this processing and cooking has the opposite effect. For example, high temperature that kills organisms also can thermally transform normal components of foods, such as proteins, carbohydrates, and lipids into toxic materials (45, 46, 47). Thus, pyridines, which are mutagenic compounds, can be formed by cooking meats. Acid and alkali treatment and fermentation processes also can result in toxic compound production (23). Data collected on toxin levels usually consists of determining whether or not particular regulatory limits have been reached. This type of data is not the type needed to predict levels of toxins that may occur during processing. Additionally, the methods used are generally not sensitive enough to detect and quantify extremely low levels of toxicants in foods (30).

In addition to the issues of toxicity and nutritional deficiencies, genetic modification has raised the issue of allergenicity of the gene product. The possibility exists to alter the structure of endogenous proteins or introduce new proteins into foods (16). One approach to determining allergenicity is to allow limited distribution and carefully monitor for allergic response (29). Other possibilities might be to use double antibody screening procedures, in which food materials (or extracts) are used as antigens to which human blood plasma (containing antibodies) is added. Complexes formed by the interaction of antibodies and antigens are detected using a second antibody labeled with fluorescent materials to bind to the initial antigen-antibody complex. This method can be used as a general means of detecting potential allergenic effects of food products (12). This approach is most useful for proteins to which sensitive individuals have already been exposed; it is not particularly useful for new proteins.

Similar to the FDA, the EPA may face analytical difficulties in their attempts to develop tolerances for pesticidal products created using the new tools of biotechnology. Historically, EPA has worked with chemical rather than biological substances. Biological pesticides have heretofore been restricted to microbial pesticides, not whole plants. Whole plants are considerably more complex than microbial pesticides, which in turn are much more complex than chemical pesticides. Identifying, isolating, and assessing the toxicity of endogenously produced pesticides creates new analytical challenges. Identifying the appropriate test material for toxicology testing, and synthesizing radioactively labeled materials to conduct metabolism studies will require the development of new methodologies.

EPA guidelines for establishing a tolerance level for transgenic plant pesticides have not yet been developed. Determining the type, nature, and level of residues in whole plants, and then testing those residues for toxicity will create analytical challenges. EPA has indicated that its assessment will focus on the pesticide product and its active ingredient, although at present, it has not clarified whether that means that EPA will regulate the gene itself, the gene product, or both. EPA also has not yet clarified

whether regulations will be applied to the seed or the whole plant.

EPA has suggested that for the purposes of product assessment, pesticidal products produced in transgenic plants might be divided into two categories—proteinaceous products and nonproteinaceous products. EPA expects that the information and data needed to assess the safety of proteinaceous products will, in general, be less than that required for nonproteinaceous products, because proteins are susceptible to acid and enzymatic digestion (56).

An example of the types of problems that may be encountered with whole plants genetically engineered to contain pesticidal compounds is illustrated by some of the technical difficulties encountered with the registration of plant extracts as pesticides. Plant extracts contain many chemical compounds, several of which maybe pesticidal. Additionally, the quantities and types of these compounds can vary substantially depending on soil type, temperature, rainfall, etc. To register plant extracts, EPA requires composition and product chemistry data for all chemical compounds in the extract. Toxicology tests representing the entire range of possible compositions must be conducted and tolerances may need to be established for all compounds (9). Needless to say, it can be time consuming, expensive, and difficult to register plant extracts as pesticides.

It is reasonable to expect that in the future, fundamental biosynthetic pathways in plants will be altered such that several potential pesticidal compounds may be present, a situation that may be analogous to plant extracts. Because EPA has not clarified its policy with respect to these types of products, it is speculative how EPA will address such products. However, if EPA does treat these biotechnology products similarly to plant extracts, this may create significant obstacles to the development of many of these types of biotechnology products.

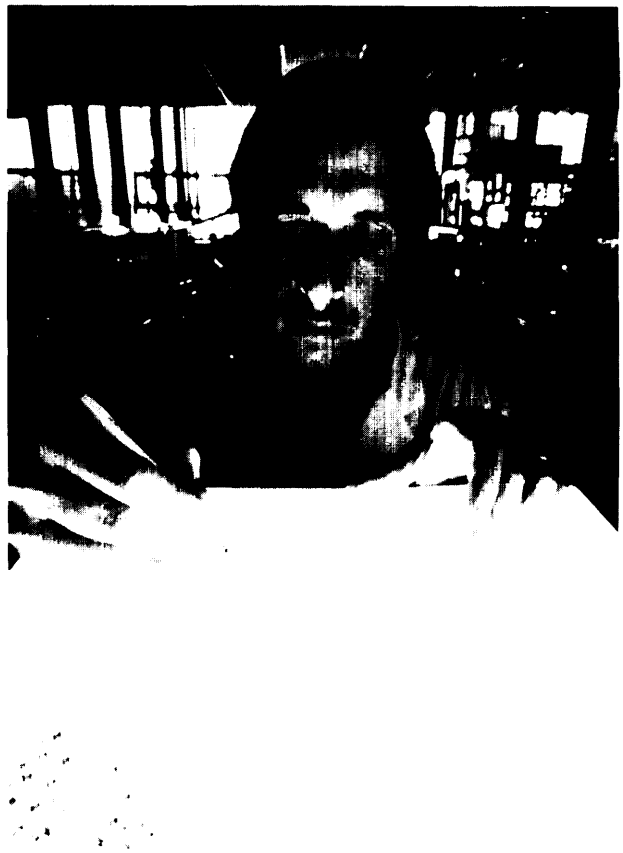


Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Chemist evaluates a screening assay for residues. New analytical methodology will need to be developed for biotechnology-derived foods.

RESEARCH NEEDS

New analytical methodology must be developed to measure the normal range of toxic and nutritional components in foods needed for comparison with biotechnology-derived foods. Whole food composition analysis is a complex task due to large numbers of potentially toxic materials that may be present in raw foods and the constantly changing nature of the processed food market. Monitoring levels of key toxic components will require a large number of assays for many different compounds, sometimes at quite low levels. Many traditional analytical methods, such as titrations and calorimetry, can be used to assay classes of compounds, such as reducing sugars or proteins, but by themselves these methods cannot be used to quantify individual members of those classes in mixtures of compounds. Food safety assays for determining individual compounds in complex mixtures are needed (30).

The analytical process starts with the preparation of the food sample followed by extraction by chemical class. Most modern analytical separation and detection techniques require clean samples free of interfering compounds. Most food samples are mixtures of multiphase materials with extremely complex chemical compositions, and the quantitative extraction of a given chemical class can be quite difficult. The development of adequate plant extraction techniques has lagged behind the other analytical techniques of food analysis. Those wishing to

use modem analytical separation and detection tools often find that the companion sample extraction techniques are inadequate, untested, or nonexistent. For example, the present methods of determining amino acid composition of foods with high sugar and starch contents is unsatisfactory-sugar and starches cause extensive losses of the amino acids in the sample preparation step (hydrolysis). The lack of proper extraction techniques is frequently the primary bottle neck to obtaining good data on the levels of the components in foods and feeds. In most cases the compounds of interest must be separated from other similar components in foods and feeds before they can be quantified. Once the extraction and separation of chemical classes has been accomplished, techniques and instrumentation for the analytical separation and detection of individual compounds are available (30).

New assay procedures must be validated before they can be widely used for food safety analysis. Validation has been defined as the process of determining the suitability of methodology for providing useful analytical data (48). Validation generally consists of 1) estimating acceptable performance parameters in a laboratory, 2) demonstrating successful performance in limited interlaboratory studies, and 3) demonstrating successful performance in collaborative studies. Performance parameters assessed include accuracy (how well the methodology measures true values), reproducibility, specificity, sensitivity (lowest levels detected), and scope (number of analytes to which the procedure can be applied (8).

New analytical methodology is needed not only to determine the initial safety of food products, but to conduct follow-up regulatory compliance and monitoring. For example, with pesticides, the toxicity of the pesticide initially must be determined. Once a pesticide is approved, methods are needed to verify that it does not exceed tolerance levels in marketed food products. Conditions under which new products are developed differ significantly from the routine conditions that exist in the day-to-day and year-to-year production and processing of foods. Genetic drift of new genetically modified species; changes in cultivation conditions or in processing conditions; and transportation or storage conditions might alter levels of toxic materials. Routine quality assurance measures should be developed. Often quick, inexpensive, and reliable analytical techniques are not available for widescale sample testing (30).

There is often a significant delay in the development of new analytical methods and their general use in food safety regulation. Nonselective, insensitive, and time-consuming assays for which validation protocols are inadequate or unavailable may be the only assays available for some compounds. New assay procedures are being developed, but they must be validated before they can be widely used for food safety regulation. Additionally, new developments in automated chemical analysis can help reduce the time and expense of manual assays. These new methods have not been rapidly adopted for food analysis, however (18, 25, 30, 43, 49, 52, 53).

Quality control and regulatory compliance personnel may work under less-than-ideal conditions, have less formal analytical training, and use less sophisticated instrumentation than food scientists working in research. The assays developed need to be rugged (i.e., require minimal training and skill on the part of the analyst and give good results even when there are small deviations from the assay protocols), completed quickly at low unit cost, and provide the necessary accuracy. Assays need to generate low levels of false positives (i.e., doesn't identify a compound as being present when it is not) and yet not have high levels of false negatives (i.e., doesn't miss compounds that are present). Assays must be accepted by the professional analytical community, regulatory community, and legal community. Formal validation usually will be required (30). In addition, compliance monitoring of genetically modified organisms may require the development of statistical sampling methods that differ for those used for pesticides and other chemical additives.

Compliance assays are particularly pertinent in that there exist no analytical techniques capable of identifying whether a food **or** feed crop has been genetically modified. Nor is it clear that any such methodology can be developed on a generic level. Development of assays for selected genetic alterations may be possible (i.e., if a given genomic sequence is known to always be present or absent in a given species, then its loss or appearance would be reasonable evidence that genetic modification had occurred). Probe technologies do exist to determine the existence or absence of specific DNA or RNA sequences and proteins, but the types of DNA sequences that conceivably could be engineered into plants is potentially great, and this procedure may not be very efficient (30).

The absence of a means of identifying if a food or feed crop has been genetically modified is made more significant by the fact that the United States imports large quantities of food and feeds yearly. The United States is by no means the only country capable of genetically modifying food crops. If the United States enacts standards that are more strict than other countries, then the general population may not feel that the assurances of

other countries is sufficient proof that the crops they are exporting are not genetically engineered. A verification methodology may be needed.

The lack of analytical systems for quality control and regulatory compliance assays of genetically modified foods and the lack of sufficient numbers of adequately trained analysts could pose major problems in the assessment of the safety of genetically modified foods. Furthermore, the training of food analysts lags far behind that of other fields (30).

Although this chapter has focused on potential food safety risks that might arise from using biotechnology to produce food products, it should be pointed out that biotechnology itself can be used to develop analytical methodologies that might improve the safety of foods. Biotechnology products can be used to monitor plant and animal products for food safety. Nucleic acid probes and monoclinal antibodies can be used to analyze raw materials, ingredients, and finished products for pathogenic organisms, bacterial or fungal toxins, chemical contaminants (i.e., pesticides, heavy metals), and biological contaminants (i. e., hormones, enzymes). Detection kits to monitor several pesticide and antibiotics, and some microorganisms such as *Salmonella,* are commercially available. Additionally, animal cell cultures may partially replace whole animal systems to test for acute toxicity. Biosensors may be used to monitor food processing, packaging, transportation, and storage (15, 39).

New analytical methodologies still are needed to assay the safety of genetically engineered foods. Such methodologies also could be used for other food-related issues, such as current attempts to analyze the anticancer properties of certain food ingredients that occur in foods such as garlic, broccoli, etc. (i.e., the designer foods project currently in progress) (40). Much research is needed to develop new methodologies. Primary attention should be given to:

- The development of acceptable alternatives to animal feeding tests for safety assessment. Because of the inability to feed high levels of whole foods to animals to determine toxicity, in vitro tests and chemical/biochemical assays need to be developed.
- The development of rapid, accurate methods for assaying food components of particular interest.
- The development of comprehensive food composition databases. It will not be possible to determine acceptable limits of variation in composition of new foods without knowing what kind of variation now exists in traditional foods.
- A greater understanding of basic molecular biology of plant development. This information will be helpful in designing genetic strategies to improve composition or food characteristics. Greater knowledge of the organization of plant genomes would be helpful in assessing the positional effects if any, Improved methods of toxicological assessment of proteins and/or whole foods would constitute an important advance in the safety review of foods.
- The development of fixed algorithms for computations and report generation to reduce the human error in food safety assessments and research.

Research must be conducted in many areas to develop the analytical methodology needed to assess the safety of food products produced with biotechnology. The regulatory agencies responsible for assuring safety must set priorities for their own in-house research programs. Additionally, it would be useful for these agencies to work with the major research funding agencies (i.e., NIH, NSF, and USDA) to support the research and training of food analysts needed to assess the safety of biotechnology food products.

SUMMARY

The key scientific issues raised by the genetic modification of foods are with respect to the activity of the inserted gene and the site of insertion of the gene into the host genetic material. Assessment of the activity of the inserted gene includes assessing the safety of the gene product itself and any secondary products whose production might be stimulated by the presence of the gene product (e. g., if the gene product is an enzyme or hormone that mediates the production of other compounds).

The gene product itself is a protein. Proteins are generally nontoxic, readily degradable in the host organism, and easily digestible by humans. The major concern with respect to the gene product itself may be that it results in increased allergenic responses rather than toxic effects. Secondary products stimulated by the presence of the gene product, however, may not be proteins. An increased understanding of plant physiology, the physiological impacts of the inserted gene, and the possible development of new analytical techniques is needed to identify any secondary compounds produced so they can be assessed for safety.

Other genetic material inserted into a host organism in addition to the selected gene might include vector

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material and marker genes used to identify those cells that incorporate the selected gene. The current use of vectors and marker genes that are well characterized, nontoxic, and already widely present in the food system is not expected to result in significant food safety problems when used to genetically modify foods.

At present, researchers cannot completely control the location where a selected gene inserts into the host's genetic material. There is a possibility that the insertion site of the selected gene will be such that it activates or deactivates host organism genes (possibly resulting in pleiotropic effects). Some host organisms used as food (e.g., most food crops, some microorganisms, and some marine animals) naturally produce compounds that could potentially display toxic effects in humans if consumed in sufficient quantity. If the insertion site of the selected gene in the host organism is such that it increases the production of these potentially toxic compounds, food safety issues could arise.

Because these insertional effects would not be predicted based on the knowledge of the physiological activity of the selected gene, one approach to detecting whether or not any of these effects have in fact occurred would be to compare the composition of the genetically modified organism with its traditional counterpart. However, our understanding and knowledge of the identity and normal levels of toxic compounds in the foods we currently eat and extraction methodologies are insufficient to perform an extensive comparison. Comparison of the levels of major nutrients and some widely known acutely toxic compounds between biotechnology-derived foods and their traditional counterparts could probably be made. But plant compounds have never been identified nor evaluated to determine if they cause long-term toxic effects in humans.

A question that must be decided is whether or not those comparisons that cannot currently be made are significant from a food safety standpoint. The development of new crop varieties using traditional breeding and cell culture techniques can also result in similar pleiotropic effects. To date, no evidence exists that the development of new crop varieties has significantly decreased the safety of the food supply. It may also be the case that new food products produced with biotechnology will present no food safety risks greater than those already generated by the foods we eat every day. It will be the task of the agencies responsible for food safety to identify those biotechnology-derived food products that may present increased food risks.

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Chapter 12

Public Perceptions of Food Safety

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Public Perceptions of Food Safety

INTRODUCTION

Public acceptance or rejection of new food products produced via biotechnology will determine the commercial success of these products. Public concerns about the food products themselves and the level of confidence in the agencies responsible for ensuring the safety of the products will be of paramount importance. Consumer demand for food safety is a relatively new research topic. Most available information consists of responses to general survey questions. Extensive empirical or statistical analyses are rare, and those that exist generally focus on issues involving pesticides. Consumer food surveys have been conducted for many years, but only recently have they included questions about food safety. The Food Marketing Institute, for example, began conducting annual opinion polls on supermarket trends in 1974, but did not include questions on food safety until 1982.

Comparisons among surveys are complicated because sampling methods, wording of the questions, and response categories provided can differ widely. Thus, direct comparisons between surveys generally is not possible. And not surprisingly, surveys that ask respondents about a specific risk report higher levels of concern about that risk than surveys that merely ask respondents to list their concerns. For example, in 1989 and 1990 the Food Marketing Institute asked consumers what they felt were the greatest risks to food safety, and also asked them to identify items they considered serious from a specified list. When asked to list food safety concerns, less than 20 percent of respondents named pesticide residues, but more than 80 percent said pesticides were a serious health hazard when specifically asked. Thus, conclusions must be viewed within the context of the questions asked (table 12-1).

The lack of commonly accepted frameworks and methods used in consumer food surveys makes it nearly impossible to arrive at many definitive conclusions concerning public perceptions of food safety. What can be reasonably deduced, however, is that over time, general concern about food safety seems to have increased (table 12-2), and the types of food risks perceived to be a problem have broadened (table 12-3). Historically, food safety concerns were commonly associated with the handling, processing, and packaging of food. These concerns still remain; however, concerns over the risks associated with the way food is grown have been added (22).

Only a handful of surveys have asked people whether new agricultural technologies, specifically those derived from biotechnology, cause any food safety concerns. While a significant percentage of consumers expressed concern about the safety of new biotechnology-derived products, a comparable percentage also expressed concern about other food safety issues, such as pesticide residues (table 12-4).

It is important not to overinterpret the results of such surveys; virtually all food contaminants are perceived as potential risks to at least some degree by the majority of consumers. However, the surveys do not ask consumers, for example, how likely it is that the contaminant is at hazardous levels in the food supply, or the probability that the level of contaminants present will result in impaired health or death to them or their family. These questions are more pertinent to assessing how concerned consumers

Table 12-1—Food Marketing Institute Consumer Food Safety Survey Responses, 1989 and 1990

	Category specified		Open-ended question	
Food safety category	1989	1990	1989	1990
			Percent	
Spoilage and germs ., ...	NA	NA	36	29
Tampering	NA	NA	20	14
Improper packaging and canning	NA	NA	17	16
Pesticide residues	82	80	16	19
Chemicals	NA	NA	11	16
Unsanitary handling by supermarket employees	NA	NA	10	11
Additives (nonspecific)	NA	NA	7	6
Preservatives	NA	NA	7	8
Unsanitary handling by supermarket shoppers	NA	NA	6	
Processing and preparations of foods	NA	NA	4	3
Pollution and environmental pollution	NA	NA	3	4
Bugs, pests, and rats ... , ... ,	NA	NA	3	3
Artificial coloring	28	21	2	3
Antibiotics	61	56	1	2
Radiation	42	42	1	1
Other	NA	NA	6	10
None	NA	NA	2	6
Not sure	NA	NA	11	12
Additives and preservatives	30	26	NA	NA
Nitrites	44	37	NA	NA

NA = Not applicable.

NOTE:
These are Food Marketing Institute (FMI) surveys of 1989 and 1990. 1989 respondents were only those that in earlier questions indicated that they were not completely confident of the food supply. 1990 respondents included everyone initially surveyed. Respondents were asked "What, if anything, do you feel are the greatest threats to the safety of the food you eat" (open ended question) and "I'm going to read a list of food items that may or may not **constitute a health hazard, For each one please tell me if you believe it is a serious health hazard, somewhat of a hazard, or not a hazard at all "**

SOURCE: Food Marketing Institute, *TRENDS: Consumer Attitudes and the Market P/ace,* **Washington, DC, 1989 and 1990,**

Table 12-2—Summary of Consumer Food Safety Surveys

	FDA	FMI	FMI	FMI	FMI	FMI	FMI	VANR
	1980	1982	1983	1986	1988	1989	1990	1991
					Percent			
Fully confident	47	NA	NA	58	55	23	15	10
Mostly confident	14	89	88	34	38	58	64	56
Somewhat concerned	28	9	11	5	5	15	18	23
Very concerned	10	NA	NA	2	1	2	2	4
Not sure/No answer	2	2	1	0.5	0.5	2	0.5	6

NA = Not applicable.

NOTES:
Food and Drug Administration (FDA) survey consisted of 1,570 respondents and asked "How do you feel about the safety of food and its effect on your health? Do you feel confident that your food is safe or do you worry about it, or what?" Response categories provided include fully confident, basically confident with some doubt, concerned about one or two specific problems, very worried, not sure.

SOURCE: James T. Heimbach, *Yesterday, Today and Tomorrow: consumer Perceptions of Food* Safety, Washington, DC, Division of Consumer Studies, Bureau of Foods, U.S. Food and Drug Administration, 1981.

The Food Marketing Institute (FMI) surveys of 1982 and 1983 consisted of 1,003 and 1,001 respondents, respectively, and asked the question "Please tell me whether you agree strongly, agree somewhat, disagree somewhat, or disagree strongly with the following statement-the food in supermarkets is safe to eat?" The results of the survey are presented in aggregate form such that the 89 and 88 percent somewhat confident figure includes both strongly agree and somewhat agree responses. Likewise, the percentages reported for somewhat concerned include the responses for both the disagree somewhat and disagree strongly categories.

SOURCE: Surveys conducted by Louis Harris Associates for the Food Marketing Institute, January 1982 and February 1983.

The Food Marketing Institute (FMI) surveys of 1986 and 1988 consisted of 1,004 and 1,019 respondents, respectively, and asked the question "The following are statements that people have made. For each one, please tell me how close it comes to describing you—very close, somewhat close, not very close, or not close at all—1 feel the food in supermarkets is wholesome and safe to eat."

SOURCE: Food Marketing Institute, *TRENDS: Consumer Attitudes and the Market Place,* Washington, DC, 1986 and 1966.

The Food Marketing Institute (FMI) surveys of 1969 and 1990 surveyed 1,031 and 1,005 respondents, respectively, and asked the question "How confident are you that the food in your supermarket is safe? Would you say you are completely confident, mostly confident, somewhat doubtful, or very doubtful?"

SOURCE: Food Marketing Institute, *TRENDS: Consumer Attitudes and the* Market Place, Washington, DC, 1989 and 1990.

The van Ravenswaay and Hoehn (VANRAV) survey consisted of 906 respondents and asked the question "How confident are you that the food your household eats is safe?" Response categories provided include completely confident, mostly confident, somewhat doubtful, and very doubtful.

SOURCE: Eileen O. van Ravenswaay and John P. Hoehn, "Contingent Valuation and Food Safety: The Case of Pesticide Residues in Food," Michigan State University staff paper No. 91-13, 1991.

Table 12-3—Specific Food Safety Concerns by Consumers[a]

	FMI						Mich	
	1984	1985	1986	1987	1988	1989	1990	1990
					Percent			
Pesticide residues	77	73	75	76	75	82	80	68
Antibiotics and hormones . . .	x	x	x	61	61	6?	56	53
Nitrites	x	x		38	44	44	37	37
Irradiation			37	43	36	42	42	36
Additives and Preservatives	32	36	33	36	29	30	26	57
Artificial colors ., ...	26	28	26	24	21	28	21	19
Tampering	x	x	x	x	x	x	x	71
Handling	x	x	x	x	x	x	x	68
Improper processing	x	x	x	x	x	x	x	67
Natural toxins and bacteria	x	x	x	x	x	x	x	50

'Respondents Indicating Serious Health Hazard

x = Not asked

NOTES:
Food Marketing Institute (FMI) surveys asked "I'm going to read a list of food items that may or may not constitute a health hazard. For each one please tell me if you believe it is a serious health hazard, somewhat of a hazard, or not a hazard at all."

SOURCE: Food Marketing Institute, *TRENDS: Consumer Attitudes and the Market Place,* Washington, DC, 1964-1990.

Michigan (Mich) survey asked "Now I'm going to read a list of factors that mayor may not constitute a health hazard to food products. For each one, please tell me if you believe the item is a serious health hazard, somewhat of a health hazard, or not at all a health hazard.

SOURCE: Charles Atkin, "Consumer Attitudes About Food Issues in Michigan," Michigan Department of Agriculture, March 1990.

Table 12-4-Consumer Response to New Agricultural Technologies

	bST				Transgenic organisms	
	VA	MO	WI	pST	**Vegetables and fruit**	**Dairy and meat**
				Percent		
Yes	44	93	71	33		82
No	19	8	NR	67	7 7	NR
Don't know	37	5	NR	NR	NR	NR

NR = Not reported

NOTES:

Surveys for **bovine somatotropin** (bST):

Virginia (VA) survey. Because only 20 percent of respondents had heard of it, they were given descriptions of the technology and conclusions of scientists concerning safety. **They were also told that it was under development and pending FDA approval. Respondents were asked if the agreed with the statement that approval of bST will make milk unsafe.**

SOURCE: W.P. Preston, A.M. McGuirk, and G.M. Jones, "Consumer Reaction to the Introduction of Bovine Somatotropin," paper presented at the Economics of Food Safety Workshop, Alexandria, VA, June 1990.

Missouri (MO) survey. Respondents were asked if they would probably or definitely have concerns about the safety of milk.

SOURCE: Barbara J. Slusher, "Consumer Acceptance of Food Production Innovations-An Empirical Focus on Biotechnology and bST," paper presented at the Second International Conference on Research in the Consumer Interest, Snowbird, UT, Aug. 9-11, 1990.

Wisconsin (WI) survey. About 90 percent of the respondents were aware of bST. Respondents were asked if they have concerns that future studies might reveal that bST might harm human health.

SOURCE: Robin Douthitt, "Biotechnology and Consumer Choice in the Market Place: Should There Be Mandatory Product Labelling? A Case Study of Bovine Somatotropin and Wisconsin Dairy Products," paper presented at the Second International Conference on Research in the Consumer Interest, Snowbird, UT, Aug. 9-11, 1990.

Porcine somatotropin (pST) survey was conducted in 1986 in Atlanta, New York City, and Philadelphia. Respondents were given a description of PST and asked if they would eat less pork due to its use in production.

SOURCE: Catherine Halbrendt et al., "Public Attitudes in the Northeast Region Toward Recombinant Porcine Somatotropin," *Journal of Food Distribution Research,* **February 1989, pp. 153–163.**

Transgenic vegetables and fruit and poultry and meat survey was conducted in North Carolina. Respondents were asked if they would be very or somewhat concerned with eating genetically engineered products.

SOURCE: Thomas Hoban. "Public Attitudes Toward Bovine Somatotropin," paper presented at the 39th Annual DairyConference, Winston-Salem, NC, Feb. 27–28, 1990.

really are about the safety of the food supply. These types of information are needed to help define what consumers mean when they say a problem is serious. Thus, surveys that report that significant percentages of consumers view a risk as serious may create the impression that consumers see huge risks from contaminants. However, this could be an erroneous conclusion. The information needed to make that type of assessment is lacking (22).

The survey information presented suggests that consumers do have food safety concerns, but it does not provide many insights into the cause(s) of these concerns. Consumer concern could be based on a real or perceived impression that the food regulatory system is inadequate. Consumers may feel that standards for safety are too lenient, have become obsolete, or are impossible to establish because of scientific uncertainty. It is possible that consumers are satisfied with the standards, but are concerned that they are not adequately enforced.

The extent of concern expressed by consumers will be influenced by their personal perceptions of risks. Risk perceptions involve assessments of the probability that loss or harm will occur as well as assessments of the type, severity, duration, and timing of the harm. Such perceptions are highly variable. Even if consumers do perceive risks, the question arises as to how much they are willing to pay to reduce or avoid a risk. Consumers are constantly evaluating these tradeoffs, and the willingness to pay to reduce risks is highly variable among the population. These issues must be understood in order to determine what food safety policy changes consumers might prefer (24).

CONCERN ABOUT THE REGULATORY PROCESS

As indicated, consumers maybe concerned that safety standards are not stringent enough, or that they are not adequately enforced. Information concerning how consumrs view safety standards is particularly pertinent as Congress debates possible changes in how the Environmental Protection Agency (EPA) sets pesticide residue tolerances. Unfortunately, definitive studies simply are not available.

There is limited information that consumers have decreased confidence in the institutions responsible for food safety. Once again, much of the information available comes from general consumer surveys (table 12-5). How-

Table 12-5—Consumer Confidence in Regulatory Agencies

	Pennsylvania		bST		PST	
	1964	1984	VA	MO	Atl	NY/Phil
			Percent			
Yes	94	49	54	51	76.7	75
No	NR	NR	NR	35	31	NR 25
Don't know	NR	NR	12	18	NR	**0**

NR = Not reported

NOTES:

Consumers in Pennsylvania were asked if they thought that the "government does an adequate job of inspection. "

SOURCE: Carolyn Sachs, Dorothy Blair, and Carolyn Richter, "Consumer Pesticide Concerns: A 1965 and 1984 Comparison," Jounal of *Consumer Affairs, vol. 21, 1987,* **pp. 96-107.**

bST (VA): Consumers in Virginia were asked if "the government will make sure milk supplies are safe and wholesome."

SOURCE: W.P. Preston, A.M. McGuirk, and G.M. Jones, "Consumer Reaction to the Introduction of Bovine Somatotropin, " paper presented at the Economics of Food Safety Workshop, Alexandria, VA., June 1990.

bST (MO): Consumers in Missouri were asked if they agreed with the statement "if a government agency such as FDA or USDA says a production process is safe then it is okay to eat foods produced that way."

SOURCE: Barbara J. Slusher, "consumer Acceptance of Focal Production Innovations-An Empirical Focus on Biotechnology and bST," paper presented at the second International Conference on Research in the Consumer Interest, Snowbird, UT, Aug. 9-11, 1990.

PST (ATL): Consumers in Atlanta were asked if they would believe Federal agencies concerning the safety of pST.

SOURCE: W.J. Florkowski, C.L. Huang, and Brian Goggin, "Attitudes Towards Porcine Somatotropin: A Consumer Survey of the Atlanta Metropolitan Area," The Georgia Agricultural Experiment Station, College of Agriculture, The University of Georgia Research Report 570, August 1989.

pST (NY/Phil): Consumers in New York and Philadelphia were asked if they would be inclined to believe Federal agencies concerning the safety of PST.

SOURCE: Catherine Halbrendt et al., "Public Attitudes in the Northeast Region Toward Recombinant Porcine Somatotropin," *Journal of Food Distribution Research,* **February 1989, pp. 153–163.**

ever, these surveys provide little information about what is causing public skepticism.

In an empirical analysis that might shed some light on this issue, van Ravenswaay and Hoehn evaluated consumer willingness to pay for pesticide labeling in apples. Using a methodology that economists call a contingent valuation study, the authors simulated market conditions by establishing a specified set of circumstances, and then asked consumers about their purchase intentions. Values obtained using this approach are contingent on, and must be interpreted in light of, the market circumstances specified. The reliability and validity of the approach depends critically on developing clear and meaningful choice scenarios, including clear descriptions of the product and conditions under which it will be offered for sale. Vague or unfamiliar choices make it difficult for respondents to predict how they would actually act, and the answers

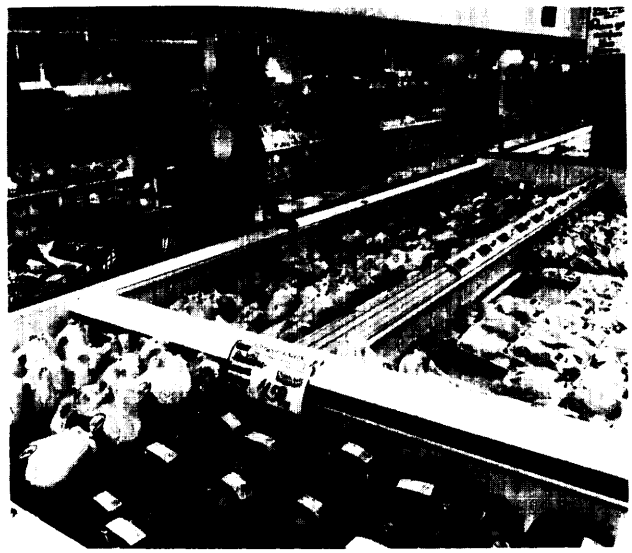

Photo credit: Grant Heilman, Inc.

Some consumers are concerned that food safety standards are not stringent enough, or that they are not adequately enforced.

given are likely to be a poor predictor of subsequent behavior (10).

The authors of the study evaluated willingness to pay for three types of product labels—no pesticide residues, no detectable pesticide residues, and no pesticide residue levels above Federal limits. Participants in the study were provided a description of pesticides and information on Federal pesticide limits. They were also informed of the circumstances under which the apples would be marketed, including the assumption that only apples would be labeled, that only one type of apple label would be available, that labeled apples would be marketed and displayed in stores as they are currently, and that the prices of substitute fruits were the prices currently prevailing at the time of the study. Consumer willingness to pay for different product labels was calculated (23).

The results indicate that on average, consumers were willing to pay 23.6 cents per pound more for apples certified and tested to have no residues above Federal limits as compared to apples with no labels. Interestingly, no statistically significant difference was found in the willingness to pay for the Federal limit label and the no detectable residue label. It was estimated that consumers were willing to pay an average of 37.5 cents per pound more for apples with the "no pesticide" label than for unlabeled apples (23).

The estimates of willingness to pay for labels provide information about how, on average, consumers value

pesticide residue reduction, and given the constraints of the methodology, the estimates represent an upper bound of willingness to pay. However, they do not tell us how many consumers would actually purchase a particular label in the market because actual purchase decisions will depend on whether or not the market conditions specified in the study prevail, and on the total price of the apples (i. e., base price of the apples plus the added price of the label) (23).

While one must be careful not to stretch the interpretation of the results too far, they do raise some interesting questions concerning how consumers feel about Federal standards and enforcement of standards. It is illegal to sell apples containing pesticide residue levels higher than Federal specifications, and as such, all apples marketed should contain residue levels that are less than the Federal limit. Yet consumers certainly demonstrated a willingness to pay for the information that the particular apple they were purchasing met Federal standards. This suggests that there is concern about the enforcement of Federal standards (23).

It is interesting that consumers were not willing to pay more for apples certified to have no detectable residues than for those that met Federal limits. Presumably, the apples with no detectable residues could have considerably lower residue levels than those that meet Federal limits. It appears that consumers are viewing these two situations as being very similar. This again suggests that consumers do not view the standards as being inadequate, but do question whether most apples actually meet the standards (23).

Consumers were willing to pay most for the “no pesticide residue” label; however, the “premium” on the “no residue’ label compared to that on the ‘‘meets Federal standards” label was much lower (13.9 cents) than the premium on the ‘‘meets Federal standards’ label in comparison to no label at all (23.6 cents). Intuitively one would suspect that if consumers were extremely concerned that the standards were too lax, that there would be a small willingness to pay for assurance that the standards were met, and a much larger willingness to pay for no residues (i.e., the differences should be the reverse of what they were calculated to be). It is possible that the difference between the ‘‘no residues’ and the ‘‘meets Federal limit” labels are simply a reflection of people’s willingness to pay more for a sure thing rather than for something that still contains some degree of uncertainty; and that in general, consumers are not unduly concerned that standards are not appropriate.

The study also found that consumer willingness to pay for labeled apples was not explained by respondents’ risk perceptions. Respondents were willing to pay more for the labels when they perceived little risk as well as when they perceived large risks from pesticide residues. A potential explanation suggested for this finding is that the method used to elicit risk perceptions measured what people think the risks are most of the time but not the level of accuracy of that assessment. People may think the regulatory system works most of the time, but that it may break down occasionally, and consumers may be willing to pay to reduce their uncertainty about these errors. This analysis implies that it is the uncertainty about risks rather than the average perception of risk that is most important to consumers. If this is so, then it implies that policy that reduces uncertainty about risks (e.g., greater sampling and testing) rather than tougher standards may be more important in alleviating consumer concerns over food safety (22).

Clearly this study does not definitively reveal the extent of consumer concern about the process of setting standards or about the enforcement of those standards. The study does, however, present insights into the kinds of information and approaches that will be needed to begin answering those questions.

PERSONAL PERCEPTIONS OF RISK

Consumer concerns about food safety will be influenced by personal perceptions of food-related risks. Risk is defined as a chance of loss or harm. The chance of occurrence can be high or low, and the potential loss or harm constituting risk can vary in type, severity, duration, and timing. A severe, lengthy, and immediate harm or loss would be viewed with greater alarm than a mild, short-term, and delayed harm or loss. This perhaps explains why consumers, in contrast to scientists and food regulatory personnel, seem to view pesticide residues as a more serious food safety risk than microbial contamination. Consumers likely associate microbial agents with an upset stomach, and possibly diarrhea, which may be inconvenient and immediate, but which is likely to be a short-term, relatively minor problem. Pesticide residues, however, are viewed as causing cancer, certainly a catastrophic illness, even though its onset may be delayed (3, 17, 23).

The concept of personal risk is further complicated by the fact that consumers can choose to take risks, or may face imposed risks (17). Risks can be avoided, but gen-

erally at some cost. If the cost of avoiding the risk is high (e.g., because there are few good substitutes available) or if a person's resources are limited, then the risk will probably cause greater distress than if the risk were easily avoided. Risks that are beyond the control of an individual may be under the control of others. If it is believed that those who do have control over risks are not seeking to minimize the risks, distrust, doubt, and suspicion could result. This may explain why some heavy smokers still become upset over any potential cancer risks associated with pesticide residues in food. Smokers choose cigarettes, but don't have much direct control over how food is produced (24).

Public understanding of risks also varies. If the probability or the type of loss involved is not clearly understood, it is more difficult for people to make decisions about whether and how to avoid a risk. A higher level of uncertainty about risks and/or the ways and costs of avoiding risks will result in a greater level of concern (24).

Thus, the possibility exists for consumers to have very different perceptions concerning food safety risks. Variation in perceptions arise primarily from four different sources. First, consumers may have different perceptions of the types, severity, duration, or timing of any adverse outcomes that may result from a risk. Second, consumers may value the same outcome differently and thus may be willing to pay different amounts to reduce the probability of that outcome occurring. Third, consumers may have different views of how likely they are to be exposed to a risk. And fourth, consumers may have a different perception of the probability that the risk will cause harm (24).

Consumer Perceptions of Adverse Outcomes

Few studies have evaluated the types of adverse outcomes consumers feel might result from food-borne risks. The little information available comes from studies that have evaluated perceived health risks associated with pesticide residues. These studies indicate that consumers do have different perceptions of the types of harm that may result from consuming pesticide residues in food. One study that compared perceptions of organic and conventional produce purchasers found that the former associated a greater number of adverse health effects with pesticide residues than did purchasers of conventional produce (6). A second study of organic produce purchasers found that these consumers considered pesticide residues responsible for a wide range of adverse health effects in addition to cancer (16). van Ravenswaay and Hoehn (22) also found that consumers differed in terms of their perceptions of the types of harms caused by pesticide residues. Thus it seems likely that consumers do have different perceptions of the types of harm that might result from food hazards.

Consumer Willingness To Pay

The types of harm consumers associate with food safety hazards are varied, and include allergic responses, intestinal disorders, reproductive problems, cancer, and possibly death. There is little information available as to how consumers value these potential outcomes, or how much they would be willing to pay to reduce the possibility of these outcomes occurring. The limited evidence that exists for how consumers value harmful food safety outcomes is obtained from studies that have analyzed conventional and/or organic food purchases. (6, 16, 23). These studies estimated the willingness to pay to reduce the annual risk of death from pesticide residues by one in a million. The estimated willingness to pay to reduce mortality by this amount was similar in all studies and for both conventional and organic produce purchasers (6). Furthermore, this estimated willingness to pay was similar to the estimated willingness to pay to achieve a one in a million reduction in mortality due to occupational hazards, or by using seat belts and installing home fire alarms (4). Thus, it appears that the willingness to pay for a reduction in mortality is similar for many consumers and is consistent for several different potential causes of death.

Consumer Perceptions of Risk Exposure

Survey data indicate that consumers do have different perceptions of the likelihood that different food items will contain pesticide residues, and generally believe that fresh produce is more likely to have residues than processed food (table 12-6). However, in the study that evaluated conventional and organic purchasers of fresh produce, the participants did not feel that different types of fresh produce presented significantly different risks (6).

Exposure to risk also depends on the cost and ability to avoid the risk. The 1989 scare over Alar in apples presents a good example. Alar was reported as posing a small additional risk of cancer particularly in children. Because there are many good substitutes for apples, consumers could easily avoid any potential risks from Alar simply by purchasing other types of fruit regardless of whether or not they believed the purported risks to be significant. Thus exposure to a risk will depend on how easily that risk can be avoided, and will vary for different individuals and food safety hazards.

Table 12-6-Consumer Perceptions of Likelihood That a Food Contains Pesticide Residues

	USDA	van Ravenswaay
		Percent
Fresh fruits and vegetables	88	5.8
Apples	NA	5.5
Lettuce	NA	5.4
Tomatoes	NA	5.2
Oranges	NA	4.8
Frozen fruits and vegetables	32	NA
Canned fruits and vegetables	28	NA
Processed fruits and vegetables (frozen and canned)	NA	4.1
Fruit/vegetable juices	NA	4.1
Dried foods (flour, cereals, rice)	*46*	NA
Cereals, flour and uncooked grains	NA	3.8
Bread and baked goods	NA	3.8
Meat and poultry	41	NA
Fresh fish	NA	4.3
Fresh meat	NA	4.2
Dairvmoducts	NA	3.1

NA = Not applicable.

NOTES:
USDA survey (1974): An in-person interview with homemakers in 2,503 households. Asked the question "Which of the types of food listed, if any, do you believe could carry traces of chemicals to kill insects and other pests?" Percentages reported are the number of respondents indicating the possibility.

SOURCE: Judith Lea Jones and Jon P. Weimer, "Food Safety: Homemakers' Attitudes and Practices, " U.S. Department of Agriculture, Economic Research Service, Agricultural Economic Report No. 360, January 1977.

van Ravenswaay and Hoehn survey (vanRav) (1990): Number of respondents was 906. Asked the question "What do you think the chances are that there are any pesticide residues in each of the following types of food that you might buy when you do the grocery shopping?" Respondents were asked to assign scores ranging from O (O = percent chance) to 10 (91 to 100-percent chance). Scores reported are the average scores for each category.

SOURCE: Eileen O. van Ravenswaay and John P. Hoehn, "Contingent Valuation Safety: The Case of Pesticide Residues in Food," Michigan State University staff paper No. 91-13, 1991.

Perceptions of the Probability of Harm

Evidence exists that different consumers view the probability of harm occurring very differently. The Hammitt study of organic and conventional food purchasers found that organic food consumers had a significantly higher estimation of the likelihood of developing cancer or other health problems than did consumers of conventional foods. This study found that organic consumers estimated that the additional risk of dying from consuming conventional produce for 1 year was 8.5 in 10,000. Conventional food purchasers estimated the additional risk of dying from consuming conventional produce for 1 year was 8 in 10,000,000. Thus, organic consumers perceive the probability of dying as being three orders of magnitude higher than conventional produce consumers. Similarly in the Rae study, organic produce purchasers estimated the additional lifetime chance of getting cancer if only organic food was eaten was 1 in 4, as compared to 1 in 2 if conventional food was eaten.

The van Ravenswaay and Hoehn study also examined consumer perceptions concerning the probability of harm. This study asked consumers to estimate the probability that current levels of pesticide residues will cause health problems to someone in your household (table 12-7). The perceptions of how likely pesticide residues are to cause health problems vary widely. When compared to worst case estimates of the cancer risks associated with pesticide residues,[1] at least half of the respondents perceived the health risks to their household as being less, approximately 30 percent view the risks as being the same, and about 15 percent consider the risks to be much higher. At least a quarter of the population perceives the risks associated with pesticide residues to be very serious, while another quarter believes them to not be serious at all. These two polar positions imply that there may be very different preferences for changes in food safety policy among consumers (24).

IMPLICATIONS FOR CONSUMER BEHAVIOR AND WILLINGNESS TO PAY FOR IMPROVED FOOD SAFETY

The food safety surveys discussed above indicate that at least 80 percent of consumers consider pesticide residues to be a ''serious' hazard; however, while data are

[1]The worst-case scenarios of lifetime additional cancer risks for an average household are estimated at 3.8 per 1,000 by the Environmental Protection Agency (EPA) and 1.6 per 100 by the National Research Council (NRC). These scenarios are based on lifetime additional cancer risks for anaverage household of 2.7 persons. For EPA, the worst-case estimate is that there would be 6,000 extra cases of cancer per year or a rate of 2 in 100,000. Assuming a 70-year lifespan and a linear dose-response function, this would be a lifetime risk of 1.4 in 1,000 persons. For a household of 2.7 persons, the household risk would be 3.8 per 1,000. Similarly, the NRC worst-case estimate of extra lifetime cancer risk from pesticide residues in food is 5.8 in 1,000. For a household of 2.7 persons, the household risks would be 1.6 in 100. The worst-case estimates and study results are not completely comparable because the worst-case scenarios looked only at cancer risks. as compared to the broader issue of health problems examined in the study. U.S. Environmental Protection Agency, "Unfinished Business: A Comparative Assessment of Environmental Problems, " 1987 and National Research Council, Board on Agriculture, Committee on Scientific and Regulatory Issues Underlying Pesticide Use Patterns and Agricultural Innovation, " *Regulating Pesticides In Food,* National Academy Press, Washington, DC, 1987.

Table 12-7—Consumer Perceptions of the Probability of Health Problems Occurring Because of Pesticide Residues in Food

	Percent
No chance	4.1
1 in a million	19.5
1 in 100,000	16.4
1 in l0,000	13.4
1 in 1,000	15.6
1 in 100	12.1
1 in 10	5.1
1 in	3.2
1 in 2	1.0
Certain to happen	4.4
No answer	5.2

NOTE:
The study asked the question "What do you think the chances are that someone in your household will have health problems someday because of the current level of pesticide residues in their food?"

SOURCE: Eileen O. van Ravenswaay and John P. Hoehn, "Contingent Valuation and Food Safety: The Case of Pesticide Residues in Food;' Michigan State University staff paper No. 91-13,1991.

skimpy, it would appear that no more than 5 to 10 percent of consumers could be classified as purchasers of organic foods (tables 12-8 and 12-9).

Given that so many consumers seem to be concerned about pesticide residues, why do so few buy organic produce? Several factors are undoubtedly involved. Organic produce may not be available in the supermarkets where consumers regularly shop. Even if available, the choice of varieties may be limited orthe organic produce maybe marketed or advertised differently from conventional produce. Another explanation may be the lackof national definitions and standards for organic produce, leaving consumers unsure about what they are actually purchasing. However, cost and quality factors also play a critical role in consumer purchasing decisions. Consumers are constantly faced with tradeoffs. For food safety concerns, a major consideration is how much it will cost to avoid or reduce perceived risks.

Because food safety is a public good required by law, consumers face few actual food safety choices in the marketplace. Consequently there are few opportunities to observe the choices and tradeoffs consumers actually make. Even if these tradeoffs could be observed, actual market choices still may not reflect willingness to pay for safety, because safety is a characteristic embodied in goods and not a separate good itself. Methodologies have been developed to overcome some of these problems so that estimates of consumer willingness to pay to reduce food risks can be made.[2] These estimates tell us how consumers value the food safety benefits of regulatory control, and what tradeoffs they are willing to make between food safety and income.

Four studies have attempted to estimate willingness to pay for reduced pesticides based on data of actual purchases or purchase intentions under specified market conditions (table 12-10). Three studies asked consumers how much they would generally be willing to pay to reduce pesticide residues without specifying market conditions (table 12-1 1). The results from the different approaches are relatively consistent with each other, and suggest that many consumers are willing to pay to reduce risks from pesticide residues, however, not all are willing to pay the same amount. Approximately one-quarter to one-third of the consumers surveyed indicate that they are unwilling to pay anything. About 5 to 10 percent of consumers, primarily those who now purchase organic foods, appear to be willing to pay premiums of up to 50 percent over conventional foods. In between are the majority who may be willing to pay 5 to 10 percent more for reduced pesticide residues (22).

Estimates of willingness to pay for reduced pesticide residues indicate what consumers may be willing to pay to reduce pesticide residues, but do not indicate whether or not consumers will actually purchase a product in the marketplace. Many factors affect the final purchase decision, including the perception of risk, total product price (price of product plus willingness to pay for added risk reduction), quality, and other factors associated with the product, such as environmental concerns, small farm issues, etc. (24).

Total price of a product will affect the quantities of the product purchased regardless of the willingness to pay for safety. For example, in the study that evaluated the willingness to pay for labeled apples, given a total price of apples of $0.79 per pound, the probability of purchase was 0.59 for no-label apples, 0.69 for Federal-limit apples, and 0.74 for no-residue apples. As total

2 TW0 methods are commonly used to estimate willingness to pay. One method seeks to reveal preferences for characteristics of goods based on examining how changes in that characteristic affect purchases of the good (a method that economists call the hedonic approach). The other method simulates the market and ascertains purchase intentions under specified circumstances (the contingent valuation method discussed previously). A third method is to simply ask consumers how much they would pay for a product improvement without describing the specific market setting or quantities involved (10).

Table 12-8—Consumers Who Have Purchased Organic Produce

	Fresh Trend	California	Michigan
		Percent	
Yes	11	62	45
No	89	38	48
Don't know	0	0	7

NOTES:
Fresh Trend Survey, October 1989, asked 1,260 households nationally if they sought or bought organically grown produce in previous 12 months.

SOURCE: The *Packer Focus: Fresh Trends 1990,* **B. Jones and T. Zind (ads.), Vance Publishing Corp., Lindolnshire, IL, 1990, pp. 37-69.**

California survey, California **counties of Marin, Sacramento, and San Diego, August 1989, asked 946 households if they purchase organic products,**

SOURCE: Desmond Jolly, "Consumer Willingness to Pay Price Premiums for Organic Apples and Peaches," Department of Agricultural Economics, University of California, Davis, March 1989.

Michgan survey was 600 households, 1990, and asked if they had ever purchased organically grown foods,

SOURCE: Charles Atkin, "Consumer Attitudes About Food Issues in Michigan," Michigan Department of Agriculture, March 1990.

price of apples increased, the probabilities of apple purchase decreased in all three scenarios (23).

Quality of the product is a major concern to purchasers of organic products. Organic products frequently have more pest damage than conventional products. Three studies have looked at how pest damage affects consumer purchases. The study that estimated consumer willingness to pay for pesticide labels in apples also estimated the amount of pest damage that would be acceptable under different label scenarios (22, 23, 24). This study presented consumers with photographs portraying apples that varied only in terms of pest damage. Four levels of damage were presented ranging from no damage to damage of 24 percent of the surface area of the side of the apple shown in photo. Respondents were asked what their purchases would be under different labeling conditions and prices. It was estimated that when the ''meets Federal limits" label was available, consumers were willing to accept damage in lieu of paying a higher price. The maximum level of damage acceptable under these conditions was estimated to be 7.5 percent of the surface area on the apple shown in the photo. For the ''no pesticide residue" level, acceptable levels of pest damage was 11.9 percent of the surface area of the apple in the photo. Since the surface area of a real apple would be larger, the acceptable level of damage is small.

Table 12-9—Frequency of Purchase of Organic Produce

	California	Michigan
	Percent	
Total purchasing organic produce	62	45
16–30 times/month	2	NA
5–15 times/month	9	NA
1–4 times/month	23	NA
less than once/month	28	NA
very often	NA	7
occasionally	NA	23
seldom	NA	15

NA = Not applicable

NOTE: Times/month is the number of times that any organic foal was purchased.

SOURCES: Desmond Jolly, Howard Schutz, Jagit Johal, and Kathy Diaz Knauf, "Marketing Organic Foods in California," Sustainable Agricultural Research in Education Program, University of Califonia, Davis, CA, August 1989; Charles Atkin, "Consumer Attitudes About Food Issues in Michigan," Michigan Department of Agriculture, March 1990.

In another study, Bunn et al. (1) presented consumers in California with three photographs of oranges. One photo presented a perfect orange, one presented an orange with 10 percent of the surface area scarred as the result of insect damage, and one presented an orange with 20-percent scarring. Seventy-eight percent of the respondents said they were less willing to buy the orange with 10-percent scarring than the perfect orange, and 87 percent were less willing to buy the orange with 20-percent scarring. When informed that the damaged oranges were grown with 50 percent less pesticide, 63 percent of respondents indicated that they were more willing to buy the orange with 10-percent scarring than the perfect orange, and 58 percent indicated they were more willing to buy the orange with 20-percent scarring.

A survey in Georgia found that 62 percent of consumers were unwilling to accept cosmetic damage to obtain pesticide-free fresh produce and 88 percent were unwilling to accept insect damage (11, 12).

Overall, these studies suggest that consumers are generally willing to accept a small amount of pest damage if they also feel that risks are reduced. However, the amount of damage acceptable is not likely to be very high (24).

Hammitt (6) found that organic-produce purchasers perceived higher risks from conventional produce than organic produce and are willing to pay higher prices for reduced pesticides (i. e., organic foods) than are conventional produce purchasers. The Van-Ravenswaay and Hoehn study that examined willingness to pay for labels, however, found that there is no strong correlation between willingness to pay and risk perception (23). This study found that consumers are willing to pay more for labels whether or not they perceived high or low risks resulting from pesticide residues. This finding suggests that even consumers that do not feel that low levels of pesticide residues pose significant risks, may have some

Table 12-10—Estimated Consumer Willingness To Pay To Reduce Pesticide Residues Under Specified Market Conditions

	Hammitt	Rae	Jolly	vanRav
	Percent willing to pay above conventional food prices			
Organic consumers	50	49	NA	NA
Peaches	NA	NA	69	NA
Apples	NA	NA	37	NA
Conventional consumers	5	NA	NA	NA
Labeled apples..	NA	NA	NA	47

NA = **Nonapplicable**

NOTES:

The Hammitt study assumes that conventional and organic versions of products differ only in terms of risk, a very strong assumption. Data was collected from shoppers patronizing two food cooperatives, one health food market, and two supermarkets in West Los Angeles and Santa Monica, CA, 1985, Estimates were based on focus group studies involving two groups each of organic and conventional produce purchasers. The values reported are the median willingness to increase expenditures over conventional produce prices to avoid a one part per million of residues. The actual observed premiums paid in the market were *45* percent higher for organic produce.

SOURCE: James Hammitt, "Organic Carrots: Consumer Willingness to Pay to Reduce Food Borne Risks," The RAND Corp., R-3447-EPA, 1986.

The Rae study was conducted in 1987 at four Bread and Circus stores in Boston. Organic produce purchasers were asked if they would be willing to support a referendum requiring EPA to eliminate the use of most pesticides if they knew it would increase the cost of food by X (20,40,50,60,80) percent.

SOURCE: Douglas Rae, "Risks of Consuming Pesticide and Fungicide Additives: Perceptions and Behavior of Organic Food Consumers," Final Report to the U.S. Environmental Protection Agency Benefits Staff, 1987.

The Jolly study involved organic fruit purchasers in Marin, Sacramento, and San Diego, CA counties in August, 1989. The estimated willingness to pay for organic apples and peaches was based on the price of conventional apples of $0.68/lb and of conventional peaches of **$0.49/lb.**

SOURCE: Desmond Jolly, "Consumer Willingness to Pay Price Premiums for Organic Apples and Peaches," Department of Agricultural Economics, University of California, March, 1989.

The van Ranvenswaay and Hoehn study was a 1990 nationwide survey. The estimate reported is for the percent increase consumers were willing to pay for apples with no label and those certified and labeled to contain no pesticide residues, given a conventional apple price of 79 cents/pound, and given that only apples (and not other produce) were labeled (thus it represents an upper bound).

SOURCE: Eileen O. van Ravenswaay and John P. Hoehn, "Willingness to Pay for Reducing Pesticide Residues in Food: Results of a Nationwide Survey," Michigan State University staff paper No. 91-18, 1991.

Table 12-1 l—Estimated Consumer Willingness To Pay for Pesticide Residue Reductions Under No Specified Market Conditions

	Atlanta	Georgia	Michigan
	Percent willing to pay above conventional food prices		
No	34	26	29
Yes	66	45	66
Don't know	**0**	29	5
How much more			
50/0	56	24	23
10%	10	15	23
0.10%	NA	6	17
Don't know	NA	NA	5

NA = Not asked

NOTES:

The Atlanta survey was administered to 313 shoppers at 9 supermarkets in Atlanta, Georgia suburbs in 1988. The survey asked if the shoppers were willing to pay more for certified pesticide-free fresh produce.

SOURCE: Stephen L. Ott and Arlyn Maligaya, "An Analysis of Consumer Attitudes Toward Pesticide Use and the Potential Market for Pesticide Residue-Free Fresh Produced," Paper Presented at the Southern Agricultural Economics Meetings, Nashville, TN, January, 1989.

The Georgia survey involved 389 members of the Georgia Consumer Panel maintained by the Department of Agricultural Economics at the Georgia Experiment Station in 1989. The survey asked the respondents if they were willing to pay more for certified pesticide-free fresh produce.

SOURCE: Stephen L. Ott, C.L. Huang, and S.K. Misra, '(Consumer Risk Perceptions About Pesticide Use in Fresh Produce Production," Paper Presented at the Economics of Food Safety Workshop, Alexandria, VA, June 1990.

The Michigan survey was a telephone survey of 600 households in Michigan in 1990. The survey asked respondents what they would be willing to pay for food products grown without the use of pesticides and/or chemicals.

SOURCE: Charles Atkin, "Consumer Attitudes About Food Issues in Michigan," Michigan Department of Agriculture, March 1990.

questions about the certainty of that perception or that the apples they are consuming may contain much higher levels of pesticides than anticipated. Thus, it would appear that consumers are willing to pay more for additional information on which to base purchase decisions.

Consumers may be willing to purchase organic foods for reasons unrelated to their perceived risks from pesticide residues. For example, purchasers of organic produce generally indicated that they bought organic products primarily for their family's health, although some consumers indicated that they bought organic products due to political or ecological concerns, concerns about small farms, and because they thought organic food was more nutritious and tasted better (6, 8, 9, 16).

IMPLICATIONS FOR NEW AGRICULTURAL TECHNOLOGIES

Unlike the development of some technologies that enhance food safety, such as refrigeration, the benefits of many biotechnology products may not be obvious to the consumer or may accrue to someone other than the consumer. For example, genetically modified enzymes may allow a food company to produce a food product at a reduced cost, but unless that reduced cost of production results in a noticeable price reduction to consumers, the benefits of the technology will not be obvious to them. Consumers may only see real or perceived increases in risk without any offsetting benefits resulting from biotechnology. If important changes in the food supply are to be introduced, industry and government regulators will have to demonstrate that risks are not going to be increased, or that there are consumer benefits that offset any added risks (14).

Risks that are uncontrollable, invisible, unfamiliar, not well understood, or involuntary will also elicit greater public concern than those that are readily identified and potentially avoided by individuals. Risks that may have catastrophic effects, affect particular groups such as children, or involve particularly dreaded diseases such as cancer will cause the most alarm. Consumers often differentiate between risks of natural and synthetic origin (21), although this distinction may not be based on any sound scientific rationale.

Industry and government regulators can help alleviate consumer fears by explaining what steps are taken to reduce any risks that exist. Additionally, offering choices to consumers can help diminish fears. Organic foods are an example. As noted, many consumers indicate that they are not willing to pay substantially higher prices for pesticide-free foods (e.g., one-quarter to one-third of consumers indicate they are unwilling to pay any price, while nearly two-thirds of consumers indicate a willingness to pay 5 percent and possibly 10 percent higher food prices). About 5 to 10 percent of consumers appear willing to pay premiums of up to 50 percent over conventional foods to reduce pesticide residues (23). Development of an organic foods market, even if prices are higher, provides consumers who can afford these prices with a choice concerning the amount of pesticide residues they are exposed to. A similar scenario may be possible with food products produced with biotechnology. Niche markets of biotechnology-free food products could be developed to satisfy those consumers whose concerns are so great that they are willing to pay potentially higher food prices to avoid biotechnology, without burdening all consumers with these potentially higher food prices.

The lack of standard frameworks and methods to analyze how consumers think about food risks, how those perceptions are affected by new information, and the tradeoffs consumers are willing to make to reduce risks, makes it difficult to assess how consumers will react to new biotechnology products. Assessments are further complicated by the fact that few consumers have heard of many of the technologies. Furthermore, of the few surveys available, the purchase scenarios given to consumers were generally ambiguous about the conditions under which the consumer would know if the product had been produced with biotechnology, what the price would be, and how the quality characteristics of the product would be affected (tables 12-12 and 12-13).

Definitive conclusions concerning how consumer purchases will be affected by the use of biotechnology in food products cannot be reached, but a few tentative conclusions are suggested by these studies. At least one-quarter of the respondents are resistant to the idea of using milk or pork produced with the use of somatotropin. However, the data also indicate that consumers revise their perceptions in light of new information regarding risks. For example, learning that the government had approved the safety of bovine somatotropin (bST) substantially reduced the percentage of consumers who said they would not purchase bST-produced milk, Price and quality characteristics also affect consumer purchase intentions. With knowledge that the price of bST- and porcine somatotropin (pST)-produced products is less than that of conventional products, a greater percentage of consumers said they would increase purchases of milk and pork produced with bST and pST. Learning that pST

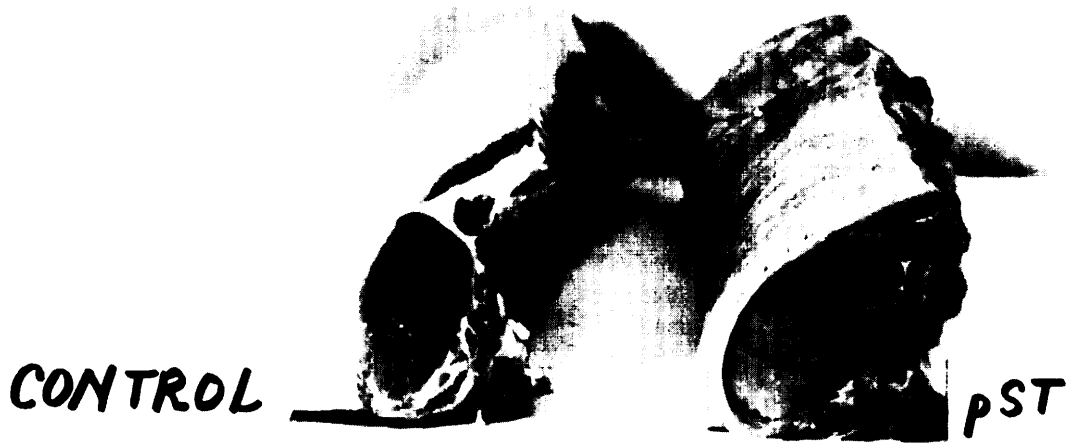

Photo credit: Terry Etherton, Pennsylvania State University

At least 50 percent of consumers surveyed are willing to pay higher prices for PST produced pork if it is leaner.

Table 12-12—Consumers Indicating Purchase Intentions of Milk Produced With Bovine Somatotropin Under Specified Conditions

	Virginia			Missouri		Wisconsin
	10¢ price decrease	40@ price decrease	No price change	bST	FDA approved	No price change
			Percent			
No change in amount purchased	79	72	82	NA	NA	**NA**
Reduce or stop purchases	16	15	16	NA	NA	**NA**
Increase purchases	4	11	NA	NA	NA	NA
Probably would purchase milk	NA	NA	NA	28	49	NA
Probably would not purchase milk	NA	NA	NA	44	28	NA
Don't know	2	2	2	28	23	NR
Prefer milk not treated with bST	NA	NA	**NA**	**NA**	**NA**	77

NA = Not applicable.

NOTES:

The Virginia study asked consumers about their purchase intentions of milk after bST was approved. Consumers were not told whether all milk or only some would be produced with bST or whether consumers would be able to identify that milk produced with bST.

SOURCE: W.P. Preston, A.M. McGuirk, and G.M. Jones, "Consumer Reaction to the Introduction of Bovine Somatotropin," paper presented at the Economics of Food Safety Workshop, Alexandria, VA, June 1990.

The Missouri study asked consumers if they would purchase milk produced with bST. They were then asked if they would purchase milk produced with bST if bST is approved by FDA. No price scenarios were given nor was it indicated whether consumers would be able to identify milk produced with bST.

SOURCE: Barbara J. Slusher, "Consumer Acceptance of Food Production Innovations-An Empirical **Focus on Biotechnology and bST," paper presented** at **the Second International Conference on Research in the Consumer Interest, Snowbird, UT, Aug. 9-11, 1990.**

The Wisconsin study asked consumers if they would prefer milk from untreated herds if milk from bST treated herds were labeled and there was no price difference.

SOURCE: Robin Douthitt, "Biotechnology and Consumer Choice in the Market Place: Should There Be Mandatory Product Labeling? A Case Study of Bovine Somatotropin and Wisconsin Dairy Products," presented at the Second International Conference on Research in the Consumer Interest, Snowbird, UT, **Aug. 9-11, 1990.**

makes pork significantly leaner resulted in more consumers indicating that they would increase purchases of pork produced with pST.

When asked if they are willing to pay more to purchase leaner pork produced with pST, 32 percent of consumers surveyed in Atlanta said they would pay 5 to 10 cents/lb extra, and 21 percent would pay even more. About half of the consumers surveyed in New York and Philadelphia indicated that they are willing to pay higher prices for pST produced pork if it is leaner. In contrast, of the consumers in Wisconsin who said that they prefer

Table 12-13—Consumers Indicating Purchase Intentions of Meat Produced With Porcine Somatotropin

	Atlanta'	New York/ Philadelphia	Atlanta/Chicago/Los Angeles New York/Philadelphia[3]
Question: Would you eat less pork if PST were used? (no price or quality information provided)			
Less likely	1570	22%	NR
More likely/yes	129'0	230/.	330/0
No change/no	420/o	550/0	670/.
Don't know	300/0	NR	NR
Question: Would you eat more pork if pST were used and the **pork is leaner?**			
	Atlanta	New York/ Philadelphia	Atlanta/Chicago/Los Angeles/ New York/Philadelphia
Less likely	14%	22%	NR
More likely/yes	27%	320/o	46%
No change/no	40%	460/o	NR
Don't know	19%	NR	**NR**
Question: Would you eat more pork if PST were used and the pork was cheaper?			
	Atlanta	New York/ Philadelphia	Atlanta/Chicago/Los Angeles/ New York/Philadelphia
Less likely	17Y0	240/.	NR
More likely/yes	21%	1 9%	44%
No change/no	43%	57%	NR
Don't know	19%	NR	NR

NR = Not reported

SOURCES:
[1] **W.J. Florkowski, C.L. Huang, and Brian Goggin,c"Attitudes Towards Porcine Somatotropin: A Consumer Survey of the Atlanta Metropolitan Area, " The Georgia Agricultural Experiment Station, College of Agriculture, The University of Georgia Research Report 570, August 1989.**
[2] **Catherine Halbrendt et al., "Public Attitudes in the Northeast Region Toward Recombinant Porcine Somatotropin," Journal of Food Distribution Research, February 1989, pp. 153-183.**
[3] **Catherine Halbrendt et al., "Socioeconomic Determinants of Attitudes Toward the Use of Bioengineered Products in Food Production," Department of Food and Resource Economics, University of Delaware, 1990.**

milk that is not produced **using** bST, 67 percent said they are willing to pay at least 5 cents more per half gallon to obtain bST-free milk.

Perhaps the feature that stands out the most in these surveys is the large number of consumers who are unfamiliar with these new technologies. Given this lack of familiarity, there is a great deal of consumer uncertainty. The greatest awareness of a new technology was for technologies that had generated controversy and media coverage in a region. Thus, 80 percent of the consumers in Wisconsin were aware of bST, while fewer than 20 percent of those surveyed in Virginia had heard of it. This implies that consumer perceptions concerning these new technologies will be affected by media coverage and controversy. The Alar scare of 1989 provides another example of how consumer perceptions can be affected by media attention. The significance of media attention and controversy is substantial given that some opponents of biotechnology have demonstrated a willingness to exploit food safety issues in their attempts to stop biotechnology.

Food Scares

Food scares can affect consumer food demand and shake the public confidence in regulatory institutions. In early 1989, reports[3] highly critical of the use of Alar (a growth regulator) in apples, followed by an alert of potential cyanide poisoning in imported grapes, lead to significant public fears over the safety of the food supply (table 12-14). Nearly a year later, the level of confidence had not recovered to previous levels.

One study isolated the effects of the Alar controversy on apple purchases by determining what the purchases would have been in the absence of the controversy (23). This difference provides an estimate of the willingness to pay for the removal of Alar. The study found that

[3] The public interest group Natural Resources Defense Council (NRDC) (18) and the television program *60 Minutes* concurrently released reports.

Table 12-14—Consumer Confidence Following Alar and Cyanide Scare

	FMI				CPQ			
	Jan. 1989	Apr. 1989	Apr. 1989	June 1989	Aug. 1989	Jan. 1990	Jan. 1989	Mar. 1989
	Percent							
Completely confident	NA	NA	NA	NA	NA	NA	25	21
Mostly confident	81	67	73	65	67	79	56	49
Somewhat doubtful	15	24	19	27	24	18	14	23
Very doubtful	2	7	6	6	6	2	4	6
Not sure , ...	2	2	2	2	3	0	NA	NA

NA = Not applicable.

NOTES:

The Food Marketing Institute (FMI) surveys were conducted in January, the second week of April, the fourth week of April, June, and August of 1989 and in January, 1990, Respondents numbered greater than 1,000 in each survey. The question asked was "How confident are you that the food in your supermarket is safe?" Response categories provided were completely or mostly confident, somewhat doubtful, very doubtful, not sure.

SOURCE: Food Marketing Institute, Consumer Confidence in Food Safety, an Update, Sept. 28, 1989 and Food Marketing Institute, "Trends: Consumer Attitudes and the Market Place," 1989 and 1990.

The Center for Produce Quality (CPQ) surveys were conducted in January and March of 1989 and consisted of 1,008 and 1,004 respondents, respectively. The question asked was "How confident are you that fruits and vegetables available to consumers are safe to eat?" Response categories provided were very, somewhat, not very, and not at all.

SOURCE: Center for Produce Quality, "Tracking Survey to Identify Changes in Consumer Concern about Pesticide Residues on Fresh Fruits and Vegetables," Produce Marketing Association, Newark, DE, April 1989.

consumers were willing to pay 21 cents per pound (a 27-percent increase) more for Alar-free fresh apples in 1989. On an annual basis and based on the average annual per-person consumption of fresh apples, this finding implies that the average consumer is willing to pay about $2.35 per year to avoid the risks of Alar. Estimates of consumer willingness to pay for a one in a million reduction in annual mortality risks were approximately the same as those calculated for other risks such as occupational hazards, seat belt use, etc. Thus consumers react to Alar in much the same way as they do to other risks, and the estimated willingness to pay to reduce Alar gives an indication of what consumers may be willing to pay to reduce pesticide risks given an unusual situation when the risks of pesticides were probably perceived to be well above what people normally believe them to be (23).

Photo credit: DNAP

Freshworld, a joint venture between DNA Plant Technology and DuPont, has been marketing VegiSnax brand carrot and celery sticks produced by plant tissue culture technology.

Food Labeling

Labels can be used to provide consumer information, and indeed, that is the primary purpose generally attributed to them. Labels as well as brands, however, are also used by the food industry to differentiate their products and to establish market niches. Labels are most frequently used for this purpose when the product is technically complex, when nutritional and food safety attributes are enhanced by processing or combining of ingredients, when advertising is important in establishing and maintaining the value of the product, and when convenience, packaging, and style are important to establishing the image of a product. When characteristics such as these are important, sellers use advertising and new product introductions to distinguish their products rather than price rivalry.

Labels may also play a role in defining public values (i.e., the choice and emphasis of information contained in labels reflects those nutritional and safety attributes considered important). Debates over the types of information that should be contained in food labels provide a forum to reach expert consensus concerning important nutrition and safety issues. Information provided on food

labels is regulated by several Federal and State agencies, and this regulation provides some public surveillance over food safety and nutrition claims (13).

Consumer surveys indicate that consumers prefer that foods derived from biotechnology be labeled as such (2, 15, 19). Consumers also prefer that foods containing pesticide residues are labeled, but studies show that even though consumers prefer labeling, they are not willing to pay significantly higher prices to get labeling. if consumers react to biotechnology products in a similar manner, then it may be reasonable to expect that they also will be unwilling to pay significantly higher prices for those labels. In general, the costs of labeling will play a significant role in consumer demand for labels. Labeling costs are born by the food industry itself (e.g., the actual costs of implementing the label), and by society as a whole (e.g., in the form of potentially higher food prices, higher taxes, fewer food choices, and a changed food industry structure).

Implementing a label change can be expensive for the food industry. Costs include administrative costs and the actual printing costs of the label itself. The cost of any analytical assays necessary to support the information contained on the label (e. g., verification of cholesterol content) and any marketing costs incurred as a result of the label change (e. g., if the label change resulted in the reformulation of a food product) must also be included in the label's cost. Additionally, any losses incurred as a result of a firm having a large inventory of products with the old label must be included (5).

Administrative costs will vary by firm size, the scope of the label change, the significance of the change, and the length of time allowed for the labeling change to occur. The scope of the labeling change can be limited (e.g., inclusion of a saccharin warning statement), or it may be comprehensive (e.g., major changes in nutrition labeling). Additionally, the number of products, firms, and industries affected will influence whether the scope of the label change is major or relatively minor. The significance of a label change can be measured, in part, by the impact it will have on the functionality of the product (e.g., the label change causes a reformulation of the product that affects the taste, texture, smell, and appearance) and on consumer perceptions of the product (5).

Analytical costs are a function of the analytical test being performed and the number of products affected. Analytical testing is the step that most frequently concerns small companies faced with a mandated label change. Large companies generally maintain their own analytical databases or contract with independent analytical testing companies to obtain lowest cost. Small companies usually produce only a few products and are often not equipped to perform analytical testing in-house (5).

Marketing costs are similar to analytical costs in that they are a function of the market test performed and the number of products tested. Firms do not regularly initiate market testing in response to labeling changes, unless a mandated label change results in a reformulation of the product that affects the characteristics of, or the public perception of the product. If major reformulations are needed as a result of a mandated label change, firms may choose to discontinue the product altogether (5).

Printing costs are a function of the printing process, the frequency with which the label must be redesigned, the complexity of the label changes, the length of time needed to implement the change, and the number of units in stock that must be changed. Label changes range from minor one-color changes to completely redesigned labels requiring extensive artwork, photography, stripping, and engraving (5).

The primary inventory cost associated with a label change is the inventory loss of old labels (i. e., products with old labels may have to be disposed of'). Many variables influence the probability and magnitude of inventory losses for a particular firm, including the average size of the inventory containing the old label, the length of the compliance period allowed for mandated label changes, the significance of the change, the size of the firm, and the type of the label (i.e., if it's a label that is added after the product is packaged, or if it is a significant part of the packaging itself). Shorter compliance periods may not be as significant for products that have short shelf lives and rapid market turnover, in contrast to products that sell more slowly in the market (5).

Mandatory changes in food labels can affect product formulation. Proponents of mandatory labeling of certain ingredients (e. g., pesticide residues) push for such labeling in the hopes that rather than stating that their product contains such an ingredient, a food processor will redesign their product so that the ingredient is not used at all. Indeed, this is one of the primary goals of Proposition 65 in California. Proposition 65 contains provisions that consumers be warned about potential exposure to certain carcinogens or reproductive toxins. Proponents hope that such labels will result in the reformulation or discontinuation of products containing ingredients requiring labels (13). Some groups have proposed that any food product that contains ingredients produced with biotechnology should be required by law to state this fact on the label (7). Many opponents of biotech-

nology hope that by requiring biotechnology labeling, food producers will avoid the use of biotechnology.

Such avoidance, in the absence of banning all agricultural biotechnology products, may be difficult to achieve. Biotechnology is not like pesticides, which are limited in number and whose residues in food, at least in theory, can be analytically verified. The numbers of genes that could be manipulated and the types of food products that could be produced using biotechnology are enormous, and at present, it is not clear if it is even theoretically possible to develop a generic assay to determine if biotechnology has been used to produce a food ingredient.

Thus, the only mechanism of verification may be intense monitoring of every step (i.e., from farm to dinner table) in the food production process. Such monitoring may be feasible in some food industries where a significant amount of vertical integration already exists (e. g., some fruits and vegetables, and poultry). For food industries that are highly decentralized (e.g., grains and oilseeds), monitoring requirements may provide significant incentives for the vertical integration of these industries. Generally, small farmers do not fare well in food industries that are highly vertically integrated. Thus, a mandatory labeling program could result in significant structural changes in agricultural production.

The record keeping and oversight needed to monitor all aspects of food production will be expensive for the food industry. Additionally, mandatory labeling programs will require State or Federal oversight, the maintenance of which will require a reallocation of personnel and tax dollars. Given that the food industry involves over two million farmers alone, in addition to millions of food haulers, processors, and retailers, effective oversight of a mandatory labeling law for all biotechnology products used in foods will not be easy to accomplish, and significant potential for abuse of the labeling requirements can exist.

Regulated voluntary labeling is an alternative to mandatory labeling of all food products containing biotechnology-derived food products. Such a policy could provide for the establishment of niche markets for biotechnology-free products. This would provide a choice to consumers who are substantially concerned about the use of biotechnology in food without unduly burdening consumers who are indifferent to the use of biotechnology in food production. As with mandatory labeling, voluntary labeling programs would require industry monitoring of the entire food production process; however, with a voluntary program, the number of firms involved could be substantially fewer than with a mandatory program (choices of food products available also may be limited). Administration of such a program would be more manageable as compared to a mandatory program, although considerable difficulties would still exist. Industry can compensate costs incurred by charging higher prices for labeled food items (i.e., similar to organic foods).

Federal or State resources will still be required to establish guidelines, provide certification or permits for participants, and to provide oversight, but these inputs will be lower than they would be under a mandatory program. Additionally, while a voluntary program is also likely to provide incentives for vertical integration, because the number of participants may be considerably less than with a mandatory program, the extent of the impact on the structure of the agricultural industry would likely be less. A regulated voluntary program would substantially shift the cost of the program to those who are most concerned about biotechnology food products, rather than requiring all of society to pay the higher prices likely to occur with a mandatory labeling program.

Alternatively, the status quo can be maintained concerning labels, with all labeling at the discretion of the food industry-hence, completely voluntary. Unlike the regulated voluntary labeling program, Federal or State regulatory agencies would not establish guidelines other than those currently in existence for food products, would not establish a certification or permit procedure, and would not conduct oversight procedures specific to biotechnology. Enforcement would be limited to the same misbranding (see ch. 10) provisions that currently exist for food products. The cost of such a program would be minimal, and it is likely that producers will limit the biotechnology information provided to consumers.

The need for information concerning biotechnology in food could be eliminated, of course, by banning the use of biotechnology in agriculture. Such a step is not without consequences, however, and even if enacted, is no guarantee that biotechnology will not be used in the food products eaten by U.S. consumers. Banning biotechnol-

[4] Firms are vertically integrated when they control two or more levels of the production-marketing system for a product. For example, a vertically integrated fruit industry could control the conditions under which the fruit is produced (i.e., varieties grown and inputs used in production) and the manner and price in which the fruit is distributed and marketed. Control of the two levels may be exercised by contractual arrangements with producers or by ownership.

ogy would greatly diminish the competitive position of U.S. agriculture, which could result in significant social costs. Some products may have significant cost advantages to farmers and processors, and if such products are available elsewhere in the world, the development of a black market trade in such products cannot be ruled out. Additionally, the United States is by no means the only country developing biotechnology for use in the food and agricultural industries. The United States annually imports billions of dollars worth of food products and seeds. Given that it may not be possible to develop verification procedures for biotechnology-derived imported foods, it is not clear how one will be able to control the importation of genetically modified food products short of banning the importation of all imported food products.

In short, contrary to the claims of proponents for mandatory labeling of biotechnology food products, such a regulation is not likely to be very low cost (7). Indeed a recent study conducted by the Wisconsin Department of Agriculture concerning a mandatory labeling program for fluid milk only (milk products such as cheese, ice cream, and yogurt were not included) produced with bovine somatotropin (bST) found that such a policy would be difficult and costly for Wisconsin to implement, and would require considerable changes in modes of operation for milk producers, haulers, processors, and distributors. Considerable funding and personnel would be needed to oversee the program. No assay methodology currently is available to detect bST in milk, making effective enforcement extremely difficult. Additionally, even if Wisconsin adopted labeling, it would be nearly impossible to control milk imported from other States. A regulated voluntary control mechanism would have some of the same problems, but they were likely to be on a smaller scale, and therefore more manageable and less costly (20).

The argument for mandatory labeling is that the consumer has the right to know whether or not biotechnology was used in the production of the food, and presumes that a high level of consumer concern will persist indefinitely. This is a possibility. It is also possible that consumers will be concerned when these products are first introduced, but as they become more familiar with the products, anxieties may decrease and the demand for labels may decline. Mandatory labeling could not accommodate this scenario; a regulated voluntary program would be more flexible in this respect.

Although a small subset of the population undoubtedly will be willing to pay higher prices to avoid products produced with biotechnology, most people will not, if they react to biotechnology as they do to pesticide residues.

SUMMARY

Attempts to study food safety issues are relatively new and do not share a standard methodology. No definitive answers to questions about public perceptions of food safety are available, but some tentative conclusions can be reached. For example, there appears to be increasing and broadening concern about food safety issues, and a general skepticism about the ability of public institutions to maintain food safety. It is not clear whether the public feels that Federal agencies establish inadequate standards of safety or inadequately enforce the standards, although some research suggests that enforcement might be the major concern. Consumer perceptions of the harm that will come from food safety risks vary extensively. While most consumers value the same harm or loss similarly, they have widely divergent views of the types of harm that might occur as a result of food safety risks, and differ significantly in their views of the probability that the risk will result in harm to them.

Because of these differences in perceptions, consumers may not be equally willing to pay for food safety precautions. For example, perhaps as many as one-third of consumers surveyed are unwilling to spend any amount to reduce risks from pesticide residues, while 5 to 10 percent of consumers surveyed appear willing to pay premiums of up to 50 percent over conventional food prices to reduce the risks of pesticides. The majority of the consumers appear willing to pay a premium of 5 to 10 percent to reduce pesticide residues. There is also evidence that consumers do consider new information about risks and change their perceptions accordingly. Additionally, when considering how much consumers are willing to pay to accept or reduce a risk, other factors, such as total product price and quality are also important decision variables. Thus, it is too early to determine how consumers will perceive food products derived from biotechnology, but it is likely that the same factors that influence their perception of the safety of conventional foods will also influence their acceptance of foods produced with new technologies. That is, the extent of safety concerns about new technologies will depend on how the potential risk is perceived, how much confidence consumers have in government food safety guarantees, how costly it is to avoid the technology, and what benefits consumers perceive will accrue to them from eating or not eating biotechnology-derived food products.

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Chapter 13

Food Safety Issues and Policy Options

Photo credit: Michael Jenkins

Contents

Chapter 13
Food Safety Issues and Policy Options

Biotechnology rekindles many of the same scientific issues concerning food safety raised by previous agricultural technologies. What is substantially different, however, is the climate in which this new class of technologies is being introduced. Society in general is more skeptical of the need for new technologies. Scientific illiteracy combined with a lack of knowledge about agriculture leads some people to misunderstand how and why biotechnologies will be used. Scandals involving institutions that develop and regulate these technologies have shaken the public's confidence in the ability of these institutions to carry out their activities responsibly. These factors lead to a high level of uncertainty among the public, and a desire for a high level of scrutiny in the development and use of new technologies. Consumers generally are willing to accept some risk if it is accompanied by a clear benefit to them. New biotechnologies that appear to or are perceived to put consumers at risk, but whose benefits accrue to someone else, are likely to meet with more consumer resistance.

The extent to which the public accepts or resists these new technologies will be influenced greatly by its confidence in the ability of the Federal regulatory agencies to protect public health and safety. Public confidence will decline if people feel that safety standards are too lax, cannot be adequately established due to scientific uncertainty, or arise through a process that is flawed or corrupt. Even if consumers have confidence that the established safety standards are adequate, they may worry about adequate enforcement. Enforcement may become more difficult if labels cannot be verified, imports increase, or if fewer or inappropriate resources are allocated to enforcement.

In addition to public confusion, uncertainty exists within industry as to how new food technologies will be regulated. After considerable delay, the Food and Drug Administration (FDA) in May 1992, released preliminary guidelines with respect to new biotechnology-derived food products. The Environmental Protection Agency (EPA) has yet to establish guidelines on data requirements needed to determine residue tolerances for pesticidal plants, and the Food Safety Inspection Service (FSIS) has not established guidelines concerning the slaughter of transgenic animals. Genetically engineered products, plants in particular, are approaching the commercialization stage at a faster rate than anticipated even 5 years ago. These agencies no longer have the luxury of long timeframes with which to articulate policy.

Uncertainty over how these products will be regulated must end. Additionally, there is a general need to regain public confidence in the regulatory agencies responsible for determining the safety of new biotechnology products. As a result of this study, OTA concludes that:

- At present consumers and producers are in limbo. Clear federal regulatory policies are needed. Preliminary FDA guidelines just released are still subject to public comments and possible revisions before receiving final approval. EPA, FSIS, and Agricultural Marketing Service (AMS) have not yet published regulations and guidelines concerning how they intend to address biotechnology food products. Both FDA and EPA need to establish scientific criteria needed to assess the safety of those products they decide to regulate.
- Public confidence in Federal regulatory institutions has been shaken. There is a general need to reestablish the credibility of these agencies so that the public will have confidence that Federal regulatory decisions concerning new biotechnology products are appropriate. Three areas that need to be addressed include: 1) public input into the decisionmaking process, 2) evaluation of the tradeoffs between industry competitive positions and the public's right to be adequately informed about health and safety issues that affect them, and 3) improved enforcement of regulations.
- Traditional approaches to food safety assessment are inadequate to assure the safety of biotechnology food products. A new food safety approach is needed. New analytical techniques must be developed.
- The United States imports billions of dollars worth of food products each year. The United States is not the only country capable of genetically engineering foods. International coordination on regulatory issues dated to biotechnology food products is imperative.

ISSUE: ESTABLISHMENT OF FEDERAL REGULATIONS AND GUIDELINES FOR BIOTECHNOLOGY FOOD PRODUCTS

Findings

In the first half of the 1980s, it was anticipated that animal biotechnologies would be developed more quickly

than plant biotechnologies because more was known about animal physiology than plant physiology. Several major scientific breakthroughs were considered necessary to speed the development of transgenic plants. Those breakthroughs have occurred, and now FDA and EPA no longer have the luxury of continuing to delay the establishment of final regulations and guidelines. Several transgenic plants are in various stages of field testing, and Federal regulatory agencies are being asked to provide advisory opinions concerning the regulatory status of these products. Transgenic plants are approaching commercialization, and scientific guidelines for assessing the safety of these plants, where required, will be needed. Continued delay in finalizing these regulations will slow the commercialization of new biotechnology products, putting American industry at a competitive disadvantage, while continuing to undermine public confidence in the ability of regulatory agencies to establish a clear policy concerning biotechnology.

As discussed in chapter 10, FDA is wrestling with whether or not to classify transgenic plants as food additives. In May 1992, FDA published a preliminary proposal regarding the regulation of new varieties of genetically modified crops. This policy states that FDA is concerned with the characteristics of the food product and not with the method used to produce the product. Thus, new genetically modified crop varieties will not automatically be required to obtain a food additive regulation. New varieties that do not contain new toxicants, elevated levels of inherent toxicants, altered nutrient composition or bioavailability, or enhanced allergenic potential may be regarded as not significantly different from conventionally produced new varieties that are generally regarded as safe. These varieties could be marketed without premarket oversight by FDA. The adulteration clauses of the Federal Food, Drug, and Cosmetic Act could be used to remove these varieties from the market if FDA disagrees with a firm's safety evaluation. Varieties that contain substances (either gene expression products or unintended products) that differ significantly in structure, function, and composition from substances currently contained in foods may be required to obtain a food additive regulation.

The lack of a priori oversight of some new varieties, however, may still leave considerable uncertainties in the minds of the public, at least for the first generation of products developed. Public confidence in the process may still require at least a minimum review of the product prior to commercial release. Such review may consist of notifying FDA of the development of a transgenic crop and provision of a minimum level of data so that FDA can make a determination as to whether a food additive petition will be needed. Such a notification process could be open to the public so that any significant concerns can be identified. Additionally, public interest groups have expressed opposition to the policy and have threatened legal action to prevent its implementation. The policy is currently open to public comment, and could be subject to revision. Congress may yet be required to intervene in the development of food biotechnology regulations if differences cannot be resolved in a timely fashion. If such action is needed, several options are available to Congress.

Policy Options

Option: Congress could monitor the development of regulations and conduct oversight hearings of FDA and EPA to determine why final regulations and guidelines do not exist and to have them report back to Congress with recommendations in these areas within a specified period of time.

This would be a strong signal to the executive branch that Congress is concerned about the delay in providing guidance to the private sector for these new technologies. An oversight hearing would provide the agencies with an opportunity to explain their rationale and concerns in establishing regulations for these new products and allow Congress the opportunity to provide guidance and direction to the agencies.

Congress and the executive branch through EPA, FDA, and USDA have a number of options for regulating transgenic organisms. The following illustrates options available.

Option: Congress or FDA could establish categorical exclusions to the requirement of a food additive regulation for certain transgenic organisms and require a case-by-case approach for the remaining products.

Essentially, this is the policy chosen by FDA. Transgenic organisms that involve gene products that are widely present in the current food supply, and do not introduce new toxicants, elevate levels of existing toxicants, alter the composition or bioavailability of nutrients, or transfer allergenic components, and that use safe marker and promoter sequences can be excluded from the need for a food additive regulation. These products do not introduce new food compounds into the food supply and they have no unintended effects. Therefore, FDA states that they can be classified as GRAS because they are equivalent to traditional new varieties that historically have been given GRAS status. Only products that contain compo-

nents that are significantly different in structure, function, and composition may be required to obtain a food additive regulation on a case-by-case basis. This option is a risk based option that requires extensive safety testing for products that are not normally found in the food supply, and less testing for products that contain substances already widely consumed. It places responsibility for the initial food safety assessment with industry. Lack of FDA oversight, especially for the first generation of biotechnology-derived food products, may raise public concerns. A number of public interest groups have indicated their opposition to this policy.

Option: Congress or FDA could establish a policy similar to the preliminary policy articulated by FDA, and include a formal notification procedure.

Such a policy would require the establishment of a system for notifying FDA when a new transgenic crop is marketed. As currently outlined, FDA policy allows firms to determine if a new variety contains components that are already widely consumed. Thus, firms can make a determination about the GRAS status of new biotechnology products without consulting FDA. In the beginning, it is highly probable that most firms will consult FDA prior to marketing a new biotechnology-derived variety, but they are not required to do so. This situation is likely to create considerable apprehension among the public. Thus, a formal system of notification may be desirable.

The notification process could include safety data the company used to determine that the product was GRAS. Such data includes the identity of the host and donor organisms, information on the genetic construct, and information on the physiology of the gene product. Additional information required could include compositional data. A comparison of nutrient and toxic component levels in transgenic and counterpart traditional crops could be included, as well as data on allergens. This type of information will be available in the development of transgenic organisms and is required for a company to make its determination of the regulatory status of the product. Thus, requiring this information to be on record with FDA should not present undue burdens on industry. However, requiring FDA to review and act on this information for all transgenic crops will place a strain on the agency's resources. Most likely FDA will need additional resources to implement this policy.

The notification process could be open to the public so that they can raise concerns and issues regarding transgenic organisms. It may also be useful for FDA to use an advisory committee to comment on the data presented. If an advisory committee is used, representatives from the public could be included along with technical representatives.

Such a policy might be effective for the safety assessment of the first biotechnology food products developed. It would allow FDA to provide at least minimal oversight over all biotechnology food products, assure the public that scientific information is available, and thus, might alleviate some public concern. In the short run, such a policy may appear to result in unnecessary regulation of these products. However, it may be the price industry must pay to have their products accepted by the public, at least in the initial stages of commercializing biotechnology food products.

Option: Congress or FDA could require a food additive petition for all transgenic crops.

This policy would force all transgenic food products to undergo a premarket safety approval process. Such a process would be tantamount to regulating the process rather than the product. It would not be based on the risks involved with the product itself, but rather would reflect a categorical determination that the process of genetic engineering is inherently risky, an assumption not established by scientific data. This policy would likely delay commercialization of transgenic crops already being developed and possibly could inhibit the development of additional transgenic crops. Such a policy, however, would not be inconsistent with a broad interpretation of the food additive definition. It probably would soothe some consumer fears and uncertainties about these products.

Option: Congress or FDA could establish some categorical exclusions of transgenic food products from the requirement of a food additive petition, and require all other biotechnology products to meet the requirements for a food additive petition.

Once again categorical exclusions might include transgenic crops that do not contain components that are significantly different from those currently present in the food supply and for which unsafe, unintended components have not been introduced. This policy would be more risk-based than requiring all transgenic organisms to meet the rigors of a food additive petition, because transgenic organisms that are essentially the same as products that have historically been viewed as safe would not be required to undergo premarket approval. This policy would ease some of the burden on industry. There may still be public apprehension with respect to those products that have been excluded.

Option: Congress or FDA could establish a policy in which the gene expression product is classified as a food additive if it would have been classified as such if added during the processing stages, and excluding from the food additive definition gene products that would not have been classified as a food additive if produced by traditional means.

A policy similar to this has been recommended by a group of food manufacturers (i.e., the International Food Biotechnology Council). Gene products that might be excluded as food additives are those that would code for agronomic functions such as drought resistance. Genes products that might be classified as food additives are those that would be considered a food additive if added during the processing stage, such as natural preservatives. However, this policy seems to be based more on the intended use of the gene product rather than any safety risk that that gene product may pose. Such a policy may be consistent with how FDA has historically interpreted the food additive amendment, but would be difficult to justify on scientific grounds.

Option: Congress or FDA could establish a policy that the need for a food additive petition be determined on a case-by-case basis for each transgenic organism.

Such a policy would allow FDA to provide oversight of all biotechnology products. This would provide the public with an assurance that all transgenic organisms would be reviewed by FDA. However, continuation of this type of policy indefinitely could overwhelm FDA, since the number of products that could be developed is large. At some point, FDA will likely need to categorize some products as GRAS, just as it does with chemical additives.

FDA is not alone in slowly establishing regulations regarding biotechnology food products; EPA has also failed to provide guidelines for establishing or exempting pesticidal biotechnology products from the requirements of residue tolerances. EPA generally exempts microbial pesticides from the requirement of a pesticide tolerance, and it is possible that microbial pesticides produced by genetic engineering techniques will also be exempted. EPA however, has not clarified how it will handle pesticidal whole plants with respect to the need to establish tolerances. Clarification is needed. Pesticidal transgenic plants are already in advanced stages of field testing, and applications to register some of these products will soon be forthcoming. Guidelines outlining what substances (e.g., the whole plant, plant extracts, single gene products) require a tolerance are needed. Additionally, because State agencies, FDA, and USDA rather than EPA enforce the tolerances, EPA needs to work closely with the appropriate agencies in establishing tolerances. EPA does meet with officials from FDA and United States Department of Agriculture (USDA). However, EPA has not adequately worked with States in establishing these tolerances.

Option: EPA may wish to hold workshops with State regulators to clarify and establish its policy position with respect to biotechnology food products.

State laws may not be compatible with EPA regulations, and some States may lack the authority or expertise to carry out EPA regulations with respect to pesticidal biotechnology products. New laws may need to be passed or old laws amended. Personnel and laboratory assay methods may need to be changed. States cannot plan for new contingencies because EPA has not kept the States informed about its intentions. In fact, it is only recently that EPA has even contracted to compile a list of contact persons in State agencies. This lack of cooperation and coordination with the States could easily lead to significant delays and difficulties with State implementation of EPA regulations with respect to pesticidal biotechnology products. Congressional hearings and oversight may be necessary if EPA does not rectify this situation.

FSIS's food safety responsibilities with respect to biotechnology products lies primarily with animal inspection. FSIS will be responsible for inspecting transgenic livestock. Transgenic livestock will not be commercially available for several years. However, transgenic research is proceeding. Given the high cost and the inefficiency of the research, many researchers would like to be able to slaughter experimental animals in which attempts to insert genes failed. FSIS plans to release guidelines in the near future concerning the slaughter of these experimental animals. Of particular interest will be guidelines concerning the slaughter and potential food use of transgenic animals that produce pharmaceuticals.

Option: Congress or EPA could establish guidelines for the safety evaluation required to establish pesticide tolerances for whole plants.

Currently, EPA does have guidelines for transgenic pesticidal microorganisms, but has yet to establish such guidelines for whole plants. Transgenic plants producing pesticidal compounds, such as Bt producing plants, are completing small-scale field trials. Guidance from EPA for dealing with such plants can no longer be delayed. Establishment of safety guidelines will require a new assessment paradigm (discussed later). Additionally, be-

cause States, FDA, and USDA enforce pesticide tolerances, EPA needs to work closely with appropriate agencies in establishing tolerances. EPA's work with States needs improvement in this area. Only recently has EPA even begun to compile a list of contact persons in State agencies. This ignoring of States could easily lead to State laws that are incompatible with Federal regulations, or to gaps in State authority or expertise to carry out Federal regulations. Congressional hearings and oversight may be necessary if EPA does not improve this situation.

Option: Congress or USDA -FSIS could establish guidelines concerning transgenic animals.

USDA-FSIS plans to release guidelines in the near future concerning the slaughter of experimental animals in which gene transfer attempts failed. Guidelines concerning the slaughter of transgenic livestock are still in early draft form. Of particular interest will be guidelines concerning the slaughter and potential food use of transgenic animals that produce pharmaceuticals. FSIS and FDA have established a joint committee to deal with issues that jointly affect the two agencies. Careful monitoring of how successful this committee is may be required.

Option: Congress may wish to monitor the development of guidelines established for the slaughter of transgenic livestock that produce pharmaceuticals.

The first transgenic livestock to be available may well be animals engineered to produce pharmaceuticals. FDA and FSIS will share food-safety responsibilities for these animals, and the two agencies have established a joint committee to deal with issues that jointly affect them. Careful monitoring of how successful this committee is may be required.

ISSUE: PUBLIC CONFIDENCE IN THE DECISIONMAKING PROCESS

Findings

One method of enhancing public confidence in the regulatory process is to make that process more open and accessible to the public. Decisions made in secret and not explained to the public often are greeted with distrust.

Opponents of increased public input in regulatory processes argue that citizens lack the training needed to understand complicated scientific and technical issues, and as such their participation only delays the agency's decisionmaking without offering any offsetting benefits. Critics also fear that public representatives may act in emotional and irrational ways and make unreasonable demands. Those who support increased public input argue that such input is invaluable in establishing the legitimacy of regulatory decisions. Indications also exist that public participation can encourage agencies to focus on a wider range of issues and values than they normally would. And, it is hard to deny public participation in regulatory processes in a democratic society.

The public will not make regulatory decisions—that is the responsibility of the State and Federal agencies whose statutory authority requires them to ensure a safe and wholesome food supply. However, public confidence that these agencies are fulfilling their responsibilities will be enhanced if there are mechanisms available for public questions and concerns to be heard and addressed prior to decisions by the regulatory agency. At present, public input into the regulatory process consists of notification and comment procedures and participation on advisory committees.

The rationale for using advisory committees is to provide expert knowledge to agencies and to enhance the credibility of their final decisions. Including public representatives in addition to technical experts and possibly industry representatives not only ensures that a broader range of issues will be addressed, it also may forestall public outcry about issues that, if aired, are not likely to raise public concerns. If the public accepts decisions because the solutions appear valid and the process was fair, industry is likely to lose less money, time, and credibility than if the decision was made based solely on industry views. Even for highly technical committees, public members force experts to express their answers in terms and concepts understandable to most people (3). However, "the public" may also include special interests who can use their membership on advisory bodies to promote private concerns. A real danger exists in allowing special interest groups to exercise undue influence on the government or to dominate advisory committees that deal with matters in which they have vested interests (3).

With these dangers in mind, Congress passed the Federal Advisory Committee Act in 1972 (5 USC app 2), which generally stipulates that the need for advisory committees must be reviewed and substantiated, that the public must have access to advisory committee meetings and all records and documents relied on by committee members, that the membership on all advisory committees be fairly balanced with respect to viewpoints and functions,

and that committees act only in an advisory capacity and be independent of agency influence. Closed sessions can be held when trade secrets or confidential commercial information is considered, for matters involving the review of investigative files, or for review of matters that would constitute an invasion of privacy. Public notice is required and public participation is encouraged. Minutes and reports must be available for public inspection (3).

The FDA uses notification and comment procedures for decisions concerning food additives and advisory committees for decisions concerning drugs. Any person may petition FDA to establish a regulation to approve the use of a food additive (21 U.S.C. 409(b)(l)). If FDA concurs that a regulation is required, it must publish a notice of that decision in the Federal Register. Any person who might be adversely affected by the proposed decision has 30 days to request a hearing. Additionally, FDA relies on input from scientific organizations, such as the National Academy of Science (NAS) and the Federation of American Societies for Experimental Biology (FASEB), and consultants for issues concerning food additives.

FDA is not required to publish the notification of the receipt of a new drug petition, except in the case of some veterinary drugs. Administration of veterinary drugs may involve release of organisms into the environment. Under such circumstances, FDA may be required to comply with National Environmental Policy Act (NEPA) requirements for public notification and comment.

Public participation in the drug approval process comes primarily from the use of advisory committees, although public participation in these committees is limited. Advisory committees advise and recommend policy, but do not make regulations themselves. Congress mandated the use of advisory committees for drugs, and currently FDA has 38 standing advisory committees most of which are concerned with human drugs and medical devices. There is one veterinary drug advisory committee. Only technical experts can be voting members of FDA advisory committees. However, industry and public representatives serve on such committees also but as non-voting members (l).

The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) requires EPA to publish a notice of receipt of any pesticide registration that involves a new ingredient or new use. EPA must also publish a notice of the receipt of any Environmental Use Permit (EUP) that is of regional or national significance. EUP's are required before pesticides can undergo field trials of greater than 10 land acres or 1 surface acre of water. Notifications are published in the Federal Register and the public has 30 days to provide written comments. EPA also publishes a notice of the issuance of pesticide regulations and EUP's. If public comments indicate that there is sufficient interest or that it would otherwise be in the public interest, EPA can hold a public hearing concerning an application.

EPA may seek additional advice concerning petitions that raise significant issues via intra- or interagency reviews and advisory committees. EPA has established a standing committee for biotechnology, the Biotechnology Science Advisory Committee (BSAC) which is composed of 9 scientists and 2 persons from the public. EPA tries to draw a distinction between truly private citizens and representatives of public interest groups (40 CFR 25.7(c)(l)(iand ii)).

The Poultry Products Inspection Act; the Federal Meat Inspection Act; and the Virus, Serum, Toxin Act do not require public comment concerning agency regulations. USDA (primarily Agricultural Plant Health Inspection Service [APHIS]) has voluntarily notified State agencies and the public when environmental releases might occur. The USDA has established a standing advisory committee for biotechnology = mthe Agricultural Biotechnology Research Advisory Committee (ABRAC), which is composed of 11 scientists and 2 lawyers. This committee advises on regulatory matters as well as research issues.

Policy Options

Option: Congress could direct agencies (FDA, USDA) to establish a mechanism to allow for increased public participation and to report its results to Congress.

This option sends a clear message to the agencies that Congress is concerned about the public's view of regulatory agencies and that the public should be more involved in the decisionmaking process. It gives maximum flexibility to the agencies to determine the method of incorporating the public's input.

A number of mechanisms are available. For example, Federal agencies could establish criteria by which local agencies can be notified any time significant risk or unique questions arise that are pertinent to them. Agencies may wish to adopt a procedure similar to that used by FIFRA, i.e., notification of petitions received, and if public interest warrants, an informal hearing. Increasing public participation will require increased resources and risk politicizing decisions, but could also enhance public confidence in the regulatory process. It might cost less in the long run.

Option: Congress could direct the agencies to increase the use of advisory committees for decisions involving biotechnology and to change the composition of their membership to increase the number of nontechnical public representatives.

For FDA, advisory committees could help establish GRAS and the minimum information needed for food additive applications of genetically engineered whole foods. These committees could be used as a first screening mechanism to see if a food additive petition is actually needed. Public meetings help assure the scientific validity of the process. EPA might also use advisory committees to establish tolerances for genetically engineered plants with pesticidal properties. This might be helpful since in-house expertise to handle this responsibility seems to be lacking. Advisory committees might also prove useful to USDA in establishing a policy on transgenic animals. The credibility of any advisory committee will be enhanced if it includes public representatives.

FDA may need to consider granting current nonvoting members of its advisory committees the right of full voting membership. And they may need to expand the list of technical fields beyond MDs from which experts are drawn.

Use of advisory committees presents some logistical problems and requires additional resources, but provides expertise that currently may be missing. Additionally, the possibility that nontechnical representatives will pursue political agendas and unnecessarily delay committee decisions exists. However, used properly, such representatives can focus the attention of the committee on issues that might otherwise be overlooked and provide legitimacy to committee decisions.

Option: Congress could direct the agencies (EPA, FDA, USDA) to change the notification procedures for advisory committee meetings.

The standard method of notification involves publication in the Federal Register. Few members of the public know what the Federal Register is, much less read it regularly. Also, notices published are written by and for those knowledgeable in the field and, thus, the general public might not recognize what the issue is. Additionally, most meetings are held in Washington, DC. Agencies could have committees convene in different cities and publish announcements, other then the Federal Register, that are more likely to be noticed by a wider public. Such activities are likely to be more expensive than current ones, however; but make the decision-making process more accessible to the public.

Option: Congress could direct agencies (EPA, FDA, USDA) to establish a mechanism to *allow for public input, even if not required by law.*

Agencies may wish to establish criteria by which local agencies and the public can be notified anytime significant risk or unique questions arise that are pertinent to them. Agencies may wish to adopt a procedure that publishes notification of petitions received, and where comments are such to indicate that there is sufficient public interest or unique questions, an informal hearing can be held.

Option: Congress could direct agencies (EPA, FDA, USDA) to increase the use of advisory committees for decisions involving biotechnology.

For FDA, advisory committees could be helpful in helping establish GRAS status and minimum information needed for food additive applications of genetically engineered whole foods. These committees could be used as a first screening mechanism to see if a food additive petition is actually needed. Also, if the meeting is public, greater assurance of the scientific validity of the process would be provided. The EPA might also use advisory committees to establish tolerances for genetically engineered plants with pesticidal properties. This might be particularly helpful since in-house expertise to handle this responsibility appears to be lacking. Use of advisory committees might also give greater credibility to USDA policy on transgenic animals, since its expertise lies mainly with inspection for microorganisms and disease rather than toxicology assessments. However, the credibility of these advisory committees will be enhanced if they include public representatives.

Option: Congress may wish to appoint a task force to study the role of independent safety testing of biotechnology products.

Independent testing is unlikely to be popular with industry. However, there is a growing perception that companies are withholding negative data, and the safety review conducted by regulatory agencies is not made using accurate and complete data. Enhanced subpoena data by the regulatory agencies, most notably FDA, could be useful. Additionally, it may be worthwhile to consider establishing independent testing of products. FDA, for example, rather than companies could choose outside investigators to perform selected safety assessments, and these contractors could report results directly to FDA rather than companies. A study to consider the broad range of implications of such a change would be warranted before implementation.

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ISSUE: TRADEOFFS BETWEEN INDUSTRY COMPETITIVENESS AND SOCIETY'S RIGHT TO BE INFORMED

Findings

Public interest groups argue that industry claims too much scientific data as confidential business information (CBI), thereby limiting the amount of health and safety data available to the public. Industry feels that there is too little protection of proprietary data, and this situation adversely affects their competitive position. Achieving the proper balance between protecting proprietary rights and disclosing health and safety data to the public is a delicate undertaking.

Disclosure practices are regulated by the Trade Secrets Act and the Freedom of Information Act. The Secrets Act (18 U.S.C. 1905) of 1982 subjects government employees to criminal penalties for the disclosure of proprietary data unless authorized by law. The Freedom of Information Act (5 U.S.C. 522(b)(4)) of 1982 permits agencies to protect trade secrets and commercial and financial information that is privileged or confidential. Both laws seek to protect information that would be of commercial value to a firm's competitor.

The FDA has restrictive CBI policies. Although Congress has mandated that health and safety testing data for new drugs can be released after another manufacturer becomes eligible to sell the drug unless extraordinary circumstances are shown (Drug Price Competition and Patent Term Restoration Act, 1984; PL98-417), little data is actually released. FDA defines extraordinary circumstances to include any claim that the data is CBI, including a claim that it could be used by competitors in foreign countries (3).

While FDA usually does not release safety data, in the case of bovine somatotropin (bST) it did. For the first time in FDA history, FDA published an article in a peer reviewed scientific journal (Science) detailing how FDA reached its conclusion that bST was safe for human consumption. Specific safety data was presented. Additionally the National Institutes of Health (NIH) and FDA hosted a scientific meeting with public participation to discuss food safety concerns of bST. Thus, FDA has shown that it can release such information when it is in the public interest.

FIFRA protects CBI, but allows release of health and safety testing data to be disclosed for registered pesticides. Also, data concerning production, distribution, sale, or inventories of a pesticide may be released in connection with a public proceeding if disclosure is in the public interest (7 U.S. C. 136h). Thus, FIFRA permits the release of health and safety data after the decision is made but not during the process.

After notification of a food additive or pesticide registration petition has been published, requests for safety data can be made under the Freedom of Information Act (FOIA). However, sometimes it is not possible for agencies to determine whether or not information is CBI in the time allotted to them to make a regulatory decision. Attempts to mitigate these problems include requesting that companies restrict their CBI claims and that they justify their claims of confidentiality at the time they submit a petition.

Currently, biotechnology firms have limited the availability of CBI involving environmental release to those public interest groups needing current information in order to participate in EPA cases. However, this condition exists because of voluntary cooperation of the firms, and this cooperation could be withdrawn at any time.

Decisions to disclose CBI focus on whether or not such disclosure will be harmful to the company. No attempt is made to weigh this harm against the public's right to be informed about health and safety issues that might affect them. Other countries, most notably Canada, have taken the approach that disclosure of health data is authorized if it is in the public interest as it relates to public health, public safety, or protection of the environment and if it clearly outweighs in importance the financial loss to the competitive position of a company or person (Access to Information Act, Canada Statute 3324).

Policy Options

Option: Congress could encourage FDA to publish more scientific review articles and hold public meetings in cases that generate public interest.

Clearly it is possible for FDA to release health and safety information to the public as they have done for bST. The public controversy surrounding this product apparently outweighed any competitive disadvantage that disclosure of this information imposed on the firms producing bST. Such a policy might prove useful in re-

sponding to public concerns about other biotechnology products and potentially could enhance the accountability and credibility of FDA decisions.

Option: Congress could conduct oversight to provide increased guidance to regulatory agencies attempting to encourage firms to reduce CBI voluntarily.

Congress could monitor whether health and safety data are being made available as products approach commercialization or if firms withdraw their voluntary cooperation and claim more data as CBI. If firms increase CBI claims, Congress could direct Federal agencies to require firms to justify CBI claims when a petition is submitted rather than waiting until a FOIA request is made. Currently, firms realize that it takes regulators longer to determine the validity of CBI claims than the time allotted to make regulatory decisions. This could encourage some firms to make CBI claims of data that in fact are not confidential.

Congress could also direct agencies to facilitate reconsideration of a decision if CBI data are released after a regulatory decision is made and causes public concern. Currently, firms can avoid disclosure of data during the regulatory process simply by claiming confidentiality and know that the regulatory decision will not be reconsidered. If the decision is allowed to be reconsidered, firms may reduce their CBI claims.

Industry will oppose increased disclosure of safety data because it will erode their competitive position. On the other hand, with the current climate of public skepticism of new technologies and regulatory agencies, increased industry accountability and public disclosure of safety data may be required of business.

Option: Congress could liberalize the CBI policy.

Congress could direct FDA to release data it is currently authorized to release but generally does not. Congress could consider adopting a regulatory policy similar to that used in Canada which would weigh any harm to the "company against the public's right to be informed about safety concerns. Current policy considers only the harm to firms. As a last resort, Congress could force the disclosure of health and safety data. Once again the potential harm to the competitive position of companies must be weighed against the public's right to be aware of potential safety risks and to regain public confidence in the regulatory process. Industry probably will object to an easing of CBI policy. Public support, on the other hand, may be equally strong for disclosure.

ISSUE: SAFETY ASSESSMENT METHODS AND REGULATORY ENFORCEMENT

Findings

Traditional food safety assessment approaches As discussed in chapter 11, are inappropriate for the assessment of whole foods because large enough quantities of the food cannot be fed to test animals without invalidating the results of the test. Thus, a new food safety approach will be required. New assay and testing methods will need to be developed and additional data concerning the normal levels of toxic compounds in foods will be needed. Additional funding will be needed to develop new testing procedures applicable to genetically modified foods.

Preliminary research indicates that a significant component of the public's lack of confidence in regulatory agencies stems from concerns that regulations are not being adequately enforced. For example, research shows that consumers are willing to pay for labels that indicate that Federal pesticide tolerances are in fact being met in apples. For Federal regulatory agencies to regain public credibility and for the public to accept biotechnology products, enhanced enforcement of regulations will need to be an integral component of the regulatory process.

Enhanced enforcement will be difficult. The regulatory agencies do not have the resources to significantly increase enforcement activities. A GAO study found that the regulatory agencies involved in food safety had less staff and funding and a larger workload in 1989 as compared to 1980. Available resources are being stretched.

In addition to the lack of available resources, the food safety regulatory agencies will need to develop new assay procedures and sampling methodologies to track genetically modified organisms. Again, studies show that FDA, for example, has not been quick to develop or adopt new practices in dealing with current food safety problems such as pesticide residues and antibiotics in milk (4, 5). Unlike pesticide residues and antibiotics, multiresidue assays methods for genetic engineering do not exist and may not be possible to construct. Generic verification that a plant has been genetically engineered will be difficult if not impossible. This creates problems in verifying the safety of imported food products unless these products are accompanied by compositional data.

Policy Options

Option: Congress could fund the development of new analytical methodologies and assay procedures through the National Institutes of Health (NIH).

New analytical methods for whole food assessments must be developed not only to determine the safety of genetically modified crops, but to monitor foods once they are marketed commercially. NIH, in coordination with FDA, could provide funding to develop food analytical technologies. These new technologies and assessment procedures would not only be useful in determining the safety of genetically engineered foods, but could also enhance several other research programs such as the designer foods project (cancer research) and nutritional programs.

Option: Congress could provide funds to NIH for the development of databases detailing the normal range of nutritional and toxic components of food.

Major nutrients and toxic substances in food have been identified, but more information is needed to assess these food components, such as the quantities at which these components are normally present in foods and their chronic impacts on humans. Assessment of such information will be needed to determine if genetically modified foods present greater safety risks than do foods currently consumed.

Option: Congress could provide additional resources to the regulatory agencies to carry out their duties.

In the absence of additional staff and funding, FDA will have a difficult time increasing enforcement activities to cover genetically modified products.

Option: Congress could direct FDA and EPA to request that assay procedures developed by firms to detect additives be readily adaptable for use under field conditions.

Currently, when firms submit a food additive petition or a pesticide registration they are required to provide an assay method to detect the residues or additive in the food. Generally, the method provided requires highly sophisticated instrumentation and is generally not compatible with multiresidue assays (i.e., the methods developed usually are single residue only). Agencies might require multiresidue assay methods that are more readily usable under field conditions than they are today. The residues would have to have some similar characteristics for a multiresidue technology to work. Development of such assay methods may create technical difficulties and are likely to create added costs to industry. However, they would improve monitoring and enforcement activities of regulatory agencies, an issue of particular importance to the public.

ISSUE: LABELING FOOD PRODUCTS IN WHICH BIOTECHNOLOGY HAS BEEN USED

Findings

Many consumers have expressed a desire for food that includes products developed with biotechnology to be so labeled. However, while consumers express a desire to have such labels, many of them are not willing to pay much for those labels. (See chapter 12.) For example, approximately one-third of consumers surveyed do not seem willing to pay anything for labels whereas another 5 to possibly 10 percent of consumers seem willing to pay as much as 50 percent higher food prices for labels. The remaining consumers appear willing to pay 5 to possibly 10 percent more for labels. Clearly a labeling proposal that is very expensive will not be popular with most consumers. Additionally, there is the problem of verification. Consumers want labels, but they want those labels to be accurate and verifiable. This is entirely consistent with the desire of consumers that current regulations be enforced. Labeling is not a substitute for an adequate safety assessment, rather it is to provide information to consumers. Labeling, unlike safety, is not a public good. The approach may be to make labeled biotechnology food products available to those willing to pay the added price of the label rather than forcing all consumers to pay higher food prices to incorporate labeling.

FDA has stated in its preliminary policy that generic labeling of biotechnology food products will not be required but selected products may require labeling. Such products may include those for which nutritional composition has been altered or potential allergens introduced. Other options are possible however.

Policy Options

Option: Congress could mandate that all food products containing constituents derived from biotechnology be so labeled.

This certainly would satisfy public desire to be aware that the food they are eating contains products derived using biotechnology. It is also likely to be very expensive and difficult to verify that food products do not contain constituents that have been derived using biotechnology. No generic means exist to identify whether a food constituent, such as a kernel of corn that will be ground into meal, has been genetically engineered or not, and it is unlikely that such a method can be developed. Thus, unlike for pesticides and antibiotics, there is no simple assay method that can be used to determine if the plant from which the corn was derived is a transgenic plant. Thus, to assure that genetically modified products are not used will require that the markets for agricultural commodities be segregated. That is not how many bulk commodities, such as grains, are currently marketed. Entirely new marketing structures will need to be developed. To guarantee the quality control of the crops will require producer oversight, which will be expensive for food processors. That added expense will be passed along to consumers. Thus, the difficulty involved in determining that a product does or does not contain any ingredients derived from biotechnology could become quite expensive. It is not clear that consumers would be willing to pay that added expense.

Option: Congress, through research and extension agencies, could encourage niche markets to be established to satisfiy the concerns of those willing to pay high prices for labeled food signifying that it does not contain genetically engineered food.

An alternative to passing the high cost of verification along to all consumers is to establish a higher priced niche market for biotechnology-free foods that would satisfy the needs of consumers who are concerned enough about biotechnology to be willing to pay higher prices for products not produced with biotechnology. Such a market would be similar to the current organic food market. Organic produce is higher priced than traditionally produced produce but provides an alternative product to consumers who are willing and able to pay higher food prices. Recent legislation has been enacted to help resolve some problems involved with organic produce, such as a lack of a standard definition, grower certification and oversight procedures, etc. Such a policy might also work for biotechnology-free food products, and would have the advantage of passing the extra costs along only to consumers willing to bear them.

INTERNATIONAL COORDINATION

The United States annually imports billions of dollars worth of food products. The United States is not the only country capable of producing biotechnology food products. If U.S. food safety regulations concerning biotechnology substantially differ from other country's regulations, several difficulties could arise. For example, if U.S. policy is substantially stricter than other countries, enforcement will be difficult. As already stated, no generic methods exist to determine genetic modification. Reliance on the word of other countries that their products contain no biotechnologically derived constituents may or may not be acceptable. Likewise, if U.S. regulations are substantially more stringent than other countries, then U.S. producers will likely be at a competitive disadvantage. If U.S. regulations are substantially less stringent than other countries, then exporting U.S. agricultural products could prove difficult. Agricultural commodities are a major export of the United States. Thus, international coordination will be an important issue. Preliminary FDA policy is consistent with the concept of the substantial equivalence of new foods discussed in the Organization for Economic Cooperation and Development (OECD) working papers and with safety assessment procedures discussed in World Health Organization (WHO)/Food and Agricultural Organization (FAO) reports.

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Chapter 14

Food Quality: The Relevance of Food Grades

PhotoCredit: Grant Heilman, Inc

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Boxes

Chapter 14
Food Quality: The Relevance of Food Grades

INTRODUCTION

Many consumers are expressing concerns over the safety and the quality of food, and these concerns extend to the use of new agricultural technology in food production. Information about food quality can be provided through labeling, brand names, price, and grades. Food grades, for example, are used to classify products according to certain quality characteristics.

The objective of a grading system is to sort a population with heterogeneous characteristics (i. e., a group of foods) into lots of more uniform or homogeneous characteristics. An effective grading system uses personal observation and testing to provide information that reduces user-perceived risks associated with product quality. Grading also aims to improve product uniformity within a particular grade and serves as the basis for price. Grading facilitates an equitable incentive system stimulating farmers to produce commodities in response to consumer preferences. As a consequence, grading transaction costs are lowered and overall marketing efficiency is enhanced. Sorting via grades also facilitates trade because many consumers are likely to lack the expertise or time to identify meaningful qualit y characteristics from heterogeneous lots of any particular commodity.

Grades for beef, fruits, and vegetables are used throughout the marketing system, i.e., by farmers, processors, wholesalers, retailers, and consumers. However, grades for some commodities (i.e,, pork) are used almost entirely at the producer-processor level. At least 70 percent of pork is cured, smoked, or further processed before it reaches the consumer, whereas most beef reaches the consumer in the fresh form; this can explain the greater need for beef quality grades at the consumer level. Pork is also more uniform from a quality point of view than beef. Most hogs are marketed at about the same age after being fed a high-concentrate diet. Beef cattle, on the other hand, may be marketed as ‘‘grass fat” or after being fed high-concentrate rations for varying lengths of time, and are slaughtered at a wide range of ages. Both factors influence tenderness and appearance of fresh beef.

The use of grades as a proxy for quality is criticized heavily for at least two reasons. First is the concern about the usefulness of current grading systems, especially for the livestock industries. The criticism focuses on the relevance of the criteria used and on the accuracy of measurement, and the value differentiation for users.

Second is the concern about the attributes on which grading is based and resulting economic incentives. For example, fruit and vegetable grades are based on characteristics that affect consumers’ senses, such as touch, sight, and taste, and on shelf-life considerations or some combination of these factors. These current sensory-based grade attributes, critics argue, indirectly may encourage the use of chemicals during the production process. For example, when the top grade of a fruit or vegetable is based on sensory characteristics, it provides economic incentive to apply chemicals so as to ensure minimal blemishes and vibrant skin color. If the standards were shifted away from sensory characteristics, fewer chemicals probably would be used because less economic incentive would exist to use chemicals.

Consumers are increasingly aware of and dubious about the use of chemicals, or chemically based ingredients, in the production and preservation of the food supply. In addition to concern that chemicals used in the production process may be deleterious to the environment, concern exists that chemical ingredients in or on food maybe injurious to human health, perhaps in ways yet unknown to the scientific community.

However, grading standards and the process of grading should not be confused with food safety. Food safety is a question of determining whether or not the ingestion of a particular food or food ingredient may be injurious to human health. Only food items already determined to be safe are graded.

This chapter focuses on two concerns 1) the usefulness of current grades and 2) the potential for alternative grade attributes. An exhaustive analysis of all grading systems is beyond the scope of this report. Instead, a case approach is used to focus on these issues. The first case study focuses on the livestock industry —specifically pork. The second focuses on the fruit and vegetable industry.

THE PORK GRADING SYSTEM[1]

USDA Grade Standards

Background

Grade standards for pork were established by the U.S. Department of Agriculture (USDA) in the early 1930s. Barrows and gilts are the primary market animals. Grades for barrow and gilt carcasses, i.e., U.S. No. 1, No. 2, No. 3, and No. 4 are based on two general considerations: 1) quality—which includes characteristics of lean and fat, and 2) expected yield (i.e., in proportion to total weight) of the four lean cuts (ham, loin, picnic shoulder, and Boston butt).

Two general levels of quality are recognized: 1) acceptable and 2) unacceptable. Presently, the quality of lean cuts is best evaluated by a direct observation of its characteristics on a cut surface. Standards indicate that when a cut surface of a major muscle is available, quality determination shall be based on the characteristics of the loin eye muscle at the 10th rib. When this surface is not available, other exposed major muscle surfaces can be used for comparable quality determinations. Generally, packers do not elect to reduce the value of a loin by cutting the loin at the 10th rib or to expose any of the major muscle surfaces. When a major muscle cut surface is not available, the quality of the lean is to be evaluated indirectly based on quality-indicating characteristics of the carcass. These include firmness of the fat and lean, amount of feathering (fat streaking in tissue) between the ribs, and color of the lean. While current standards employ feathering as a quality indicator, there is no scientific evidence that feathering is related to quality.

A barrow or gilt carcass with acceptable lean quality and belly thickness is placed in one of four grades, depending on the backfat thickness over the last rib, and the degree of muscling (thickness of muscling in relation to skeletal size). These two factors together indicate the expected carcass yields of the four lean cuts. These yields are based on cutting and trimming methods used by the U.S. Department of Agriculture in developing the standards (table 14-1). Other cutting and trimming methods may result in different yields.

Adoption of USDA Grades

Use of USDA grade standards is voluntary. However, if a packing plant decides to use grade standards and designate the U.S. grade on a package label, they must use USDA's grade standards.

A USDA study of 12 packers in 1981 and 1982 found that none of the plants used the USDA grading system (66). This may be attributable in part to the fact that USDA grade standards had not changed since 1968, whereas the characteristics of the market hog population had changed significantly. In 1981–82, 71.7 percent of the market hogs were graded U.S. No. 1, and 24.4 percent were graded U.S. No. 2; these USDA standards were not effectively discriminating among hogs varying significantly in value. Most packers developed their own grading systems in order to differentiate among pork carcasses (one plant had no grading system). Because each packer's grade and evaluation system was individually designed, grade criteria, descriptive terms used for grades, and evaluation methods varied among packers. Among the factors used to determine grading standards were backfat, muscling, percentage of carcass weight consisting of primal cuts, and conformation. Packer employees primarily used visual appraisal for grading. In 1985 the USDA changed the backfat standards for its grades (table 14-1), but a study of market hog characteristics from five plants in the South and Midwest predicted that 98 percent of the pigs would be in the U.S. No. 1 or No. 2 grade (52). Thus, USDA grades still do not adequately differentiate carcass quality. Overall, pork carcass characteristics have improved to where most meet the standards for the top USDA grades.

Packer grading and evaluation systems also have evolved over the past decade and now have little in common with the USDA grading system. A 1990 Iowa State University survey of 12 of the largest pork slaughter firms found that all large packers now are using carcass weights in their evaluation procedure. Four of the largest packers indicated that actual backfat measurements were the primary basis for their internal evaluation system and their carcass merit buying systems (though the grade could be modified by extremes in muscling noted by visual evaluation). Where backfat measurements were employed, the top grades often had much lower backfat thresholds than USDA grades currently do, with one at 0.6 inches of backfat or less, and two at 0.8 in. or 0.75 in. or less. Seven firms reported currently using or switching soon to the use of the Fat-o-Meter, which calculates percent lean in the carcass from the backfat measurement (taken 2½ inches off the midline of the carcass at the 10th rib)

[1] This analysis is based on the OTA commissioned background paper "An Analysis of the Pork Grading System: Needed Adjustments, " by James Kleibenstein, Marvin Hayenga, Lauran Christian, Kenneth Prusa, Robert Rust (all associated with Iowa State University); and John Forrest, AlIan Schinckel and Max Judge with Purdue University (31).

Table 14-1—Expected Yields of the Four Lean Cuts, by Grade, Based on Chilled Carcass Weight[a]

Grade	Yield
U.S. No 1	60.4 percent and over.
U.S. No 2	57.4 to 60.3 percent.
U.S. No 3	54.4 to 57.3 percent.
U.S. No 4	less than 54.4 Percent.

*These yields will be approximately 1 percent lower if based on hot carcass weight.

SOURCE: U.S. Department of Agriculture.

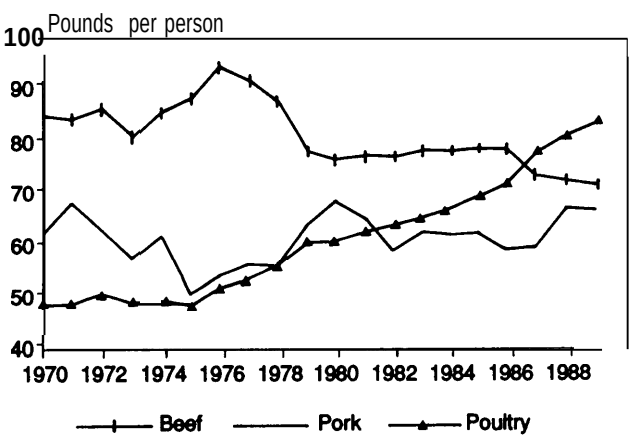
and the loin muscle depth at that location. The percent lean in the carcass then serves as the basis for grading.

In summary, the current USDA pork carcass grading system already is significantly out of step with industry systems: changes in pork carcass composition brought on by new growth promotant technologies may cause further divergence of government and industry grading systems. The USDA pork grades are primarily employed in Federal-State market news and price reporting for live hogs rather than in packing plants. This contrasts with the USDA beef grading system, which is used extensively by beef packing plants for price reporting. In 1989, the American Meat Institute reported that 56 percent of the beef produced was quality-graded, and 65 percent was yield-graded using USDA standards.

Changing Public Concerns and Expectations

Annual per capita consumption of red meat has been declining (figure 14-1) as poultry and fish have been substituted for red meat. The dramatic increase in poultry consumption reflects the aggressive marketing of poultry products, their lower relative price, and the response of consumers to fat and cholesterol concerns. Consumption of all meat has trended upward overtime. Total per capita consumption of red meat and poultry reached a record level in 1989 of 220 lbs. per capita, compared with 200 lbs. in 1970 and 170 lbs. in 1960 (figure 14-1). While annual per capita consumption of pork varies cyclically in the United States, there has been little change in pork consumption levels over the long term. Annual per capita consumption of beef, however, has declined dramatically; from 94.2 lb. in 1976 to 71.0 lb. in 1989.

Figure 14-1—Per Capita Pork, Beef, and Poultry Consumption, United States, 1970-1989



SOURCE: U.S. Department of Agriculture.

Consumer preferences and attitudes *regarding* meat products have a major influence on meat and meat product demand. Consumer perceptions of product quality and healthfulness, product convenience, cultural or ethnic background, household age composition, lifestyle, and price all impact purchase decisions. Health concerns related to fat and cholesterol levels can affect some consumers' attitudes and preferences regarding pork and beef. These have likely led to changes in demand for meat products. These shifts are difficult to measure accurately, and their impact on purchase patterns are not well documented; it seems likely, however, that health and diet issues will be major factors influencing the future demand for pork and beef. In addition, the need for better nutritional labeling on food products is receiving attention. Healthfulness of food products may be a major driving force in future food policy and consumer purchasing decisions.

A series of Food Marketing Institute (18, 19, 20) consumer surveys document the evolution of factors influencing consumer food purchases. Taste is clearly the leading factor, with 90 percent of consumers surveyed in 1991 considering it very important, and 8 percent somewhat important. Nutrition, product safety, and price ranked high, with 71 to 75 percent of shoppers considering each very important.

At various times nutrition has not been so important to consumers. In 1983, 64 percent of supermarket shoppers were very concerned about nutrition, whereas in 1987, 54 percent indicated this level of concern, and 40 percent were somewhat concerned. In 1991, 75 percent of shoppers surveyed considered nutrition very important, with 22 percent considering it somewhat important in food selection. In food selection decisions, concern about overall nutritional issues is being replaced by concern for specific nutritional components, such as (in order of decreasing importance) fat content, cholesterol level, salt content, calories, vitamin/mineral content, and pre-

servatives (20). Some of those specific concerns were evident in the 1983 survey as well.

Preservatives and chemical additives used in food preparation have emerged as a major consumers concern in recent years. In 1991, 80 percent of shoppers surveyed considered chemical residues in foods a serious hazard (20). The presence of antibiotics and hormones in poultry and livestock feeds was ranked as the second most serious hazard (56 percent). Irradiation was viewed as a serious hazard by 42 percent of the respondents, closely followed by nitrites at 41 percent.

A recent National Research Council report indicates that Americans consume too much fat with consequential nutrition-related health problems (41). A common method to reduce fat in meat products is trimming. Perhaps a more efficient method is the production of leaner animals (41). The pork industry has attempted to reduce the fat content in fresh pork significantly through selective breeding (genetics) and diet and management practices (58). Technological advancements, such as growth promotants and application of genetic engineering, offer the opportunity to markedly improve body composition of pigs before slaughter.

Consumers also are increasingly desirous of product uniformity. While level of desired quality varies among consumers, an individual consumer typically prefers products of uniform quality, as exemplified by the success of many fast-food establishments such as McDonald's, Wendy's, Kentucky Fried Chicken, etc. A visit to the local meat counter, on the other hand, illustrates the lack of uniformity in pork products—present grading systems do not directly reflect product quality.

New *Technologies and Implications for Pork Grading*

A young animal develops lean muscle more rapidly than fat; but as the animal matures, fat accumulates more rapidly than lean. With increasing consumer concerns about fat, it is advantageous for pork producers to shift the growth pattern away from fat accumulation to lean tissue accumulation, particularly during the finishing phases of production. In pork production, recombinant porcine somatotropin (pST) and beta-agonist administration (discussed in ch. 3), shifts the growth response from fat accumulation in pigs to deposition of lean tissue.

Porcine Somatotropin

As discussed earlier, carcass characteristics such as backfat thickness and carcass weight currently determine USDA carcass grade. Thus, changes in the carcass composition that result from use of pST or beta agonists can impact the present grading standards.

Table 14-2—influences of pSt or Ractopamine on Production and Carcass Characteristics of Pigs[a]

	pST[b] (in percent)	Ractopamine[c] (in percent)
Feed efficiency	+21 .1	+ 12.7
Average daily gain	+ 15.2	+ 8.4
Average backfat	– 24.8	– 15.3
Loin eye area	+ 18.5	+ 16.3
Muscle mass	+ 9.9	+ 9.3
Carcass yield[d]	-2.4	+ 1.4

[a]Expressed as an increase or decrease as compared with controls,
[b]Summary of 20 research trials.
[c]Summary of up to 17 research trials.
[d]Hot carcass weight divided by live weight X 100.

SOURCE: D. Zimmerman, "Growth Enhancers," Proceedings on New Swine Growth Enhancers, Iowa State University, 1989.

Zimmerman (70) summarized the available studies that evaluated the impact of pST administration on lean meat production and feed efficiency (table 14-2). The magnitude of response of pST administration varies from study to study and depends on frequency of administration, pST dose level, time of administration, genotype, gender, energy intake, and protein and amino acid intake.

In 20 research trials evaluated by Zimmerman, pST was injected daily at dosages from 15 to 100 ug/kg body weight. Pigs weighed 40 kg or more at the beginning of the treatment period and were fed a diet containing at least 16 percent protein. In many cases diets were supplemented with additional lysine. The average daily gain of pST-treated pigs was 15.2 percent higher than that of controls. Feed efficiency was 21.1 percent higher.

The use of pST has a positive impact on most carcass characteristics. Average backfat thickness decreased by 24.8 percent, loin eye area increased by 18.5 percent, and quantity of muscle mass increased by 9.9 percent with pST administration. In general, the carcass percent lean, which was 52 percent for control pigs, was 64 percent for pST pigs (4); the actual differential depended on the level of pST administered. Studies have shown percent lean increases of 15 to 25 percent. Dressing percentage (carcass yield) decreased by 2.4 percent when pST-treated pigs were compared with controls.

A rapidly accumulating body of data indicates that administration of pST to finishing pigs alters the yield and distribution of wholesale cuts in the carcass. Weight and percentage of lean cuts are significantly increased (ham, 12 percent; loin, 11 percent; Boston butt, 12 per-

Photo credit: Terry *Etherton, Pennsylvania State University*

Comparison of pork loins that show the effect of pigs treated with porcine somatotropin **(pST).** The **loin-eye area of the loin treated with pST is 8 square inches; the control is 4.5 square inches.**

cent; picnic, 9 percent) whereas weight and percentage of fatty cuts are reduced significantly (belly, 13 percent; jowl, 32 percent) (6, 12).

Proximate composition of the skeletal muscle exhibits a dose-dependent decrease in lipid concentration and a small but significant increase in protein concentration with pST administration (5, 6, 39, 47, 48). Cholesterol concentration of the loin muscle is not altered, and only minor increases in percentage of polyunsaturated fatty acids are observed in the subcutaneous or intramuscular fat of pST-treated pigs (6).

Although data are sparse, little indication exists of any change in mineral concentrations (22) or vitamin content of muscle (46) with administration of pST. Therefore, the most significant effects of pST on nutrient composition of edible tissues is reduction of neutral lipid concentration. Several investigations indicate that cooking loss and sensory characteristics of fresh pork are not adversely affected by pST administration, unless very high doses are administered (5, 6, 15, 22, 47, 64).

In a study that evaluated consumer reaction to pork from pigs treated with pST, nearly 1,200 consumers sampled broiled loin chops from pST-treated and control pigs. Pork from pST-treated pigs was favored by 58.8 percent of the participants for its tenderness, by 60.6 percent for its juiciness, and by 53.7 percent for flavor (49).

In another study, members of 114 Des Moines households (414 people) compared boneless loin roasts from pigs treated with and without pST (17). Overall, no difference was noted in how individuals liked the two roasts. Roasts from pST-produced pigs were judged larger and leaner than control roasts.

pST On-Farm Study

Most studies of pST's effects on pork production and carcass characteristics have been conducted within an experimental and control setting. The expected production responses to pST under normal farm conditions were studied on 15 Iowa pork production operations (50) at Iowa State University. Some pigs were grown to the normal market weight (109 kg) while others were taken to 131 kg before marketing.

The administration of pST had a dramatic positive effect on packer-determined carcass grades (table 14-3). Only 18 percent of control carcasses graded No. 1, whereas 41 percent of the pST (109 kg) group and 69 percent of the pST (131 kg) group graded No. 1. Over 90 percent of the pigs administered pST graded a No. 3 or better, versus only 75 percent of the control hogs. Even though allowances were made for increased backfat with heavier weight pigs a substantial improvement in grade was noted with pST use. However, dressing percentage (hot carcass weight as a percent of live weight) was depressed slightly due to pST administration (table 14-4).

Beta-Agonists

Zimmerman (70) also summarized the large number of research trials that have involved the use of ractopamine in finishing pigs (table 14-1). As with pST, re-

Table 14-3—Effect of Porcine Somatotropin (pST) Administration on Pig Growth Performance

Treatment[a]	Control/ 109 kg (n = 15)	pST/109 kg (n = 12)	ST/131 kg (n = 13)
Start weight (kg)	69.3	69.0	69.3
Final weight (kg)	109.3	111.5	126.3
Gain (kg)	40.0	42.6	57.4
Feed (kg)	144.3	125.6	173.5
Feed/Gain	3.6	3.0	3.0
Average daily feed (kg)	2.7	2.4	2.4
Average daily gain (kg)	0.76	0.81	0.79

[a]**control/109 kg targeted for slaughter at 109 kg, a summary of 15 farms averaged over 533 pigs; pST/109 kg targeted for slaughter at 109 kg, a summary of 12 farms averaged over 373 pigs; pST/131 kg, targeted for slaughter at 131 kg, a summary of 13 farms averaged over 437 pigs.**

SOURCE: K. Prusa et al., 'Influence of Porcine Somatotropin (pST) on Carcass Characteristics of Pigs—A Summary of 15 Producer Trials," *Journal of Animal Science 69:344, 1991.*

sponses were found to vary from study to study. In general the trials utilized 20 ppm of ractopamine and at least 15 percent protein in the diet, and all experiments were based on starting weight of approximately 60 kg and ending weights of 105 kg body weight. Averaged over all trials, ractopamine increased average daily gain by 8.4 percent and feed efficiency by 12.7 percent when compared with control pigs. Research of Veenhuizen et al. (67) and Anderson et al. (1) shows feeding beta-agonists increases growth rate and feed efficiency, decreases backfat, and increases loin muscle size of pigs.

The use of ractopamine also has a positive effect on carcass characteristics. Backfat was decreased by 15.3 percent, loin eye area increased by 16.3 percent, and muscle mass increased by 9.3 percent. In general, carcass percent lean increased from 51 percent to 57 percent when 20 ppm of ractopamine were administered (69). When lower levels were administered, response rates were lower. Similarly to pST, ractopamine increases the weight and percentage yield of trimmed wholesale cuts (ham, 7 percent; loin, 6 percent) (36).

In contrast to pST, ractopamine increased carcass yield by 1.35 percent; and beta-agonist use did not significantly reduce the amount of intramuscular fat in lean tissue. Animals fed cimaterol (68) or ractopamine (36) had the same intramuscular fat contents in their loin muscle as control pigs. Lee et al. (33) found that ractopamine feeding had only a minor effect on fatty acid profiles in adipose tissues of finishing pigs, and Walker et al. (68) found no differences due to cimaterol treatment in the total saturated-unsaturated fatty acid ratio of the subcutaneous fat. These researchers also reported that cimaterol had no affect on carcass fat firmness scores or intramuscular fatty acid profiles.

Little information about the sensory quality of pork from beta-agonist-supplemented pigs is available. Greater Warner-Bratzler shear values (toughness) of the loin increased in pigs that received cimaterol treatment in the range of 0.50 to 1.0 mg/kg (28, 68). Effects of beta-agonists on pork quality may be compound specific (36) because ractopamine feeding had no effects on the tenderness, juiciness, or flavor of fresh or cured pork.

In summary, pST and beta-agonist administration improves feed efficiency and average daily gain reduces

Table 14-4-Effect of Porcine Somatotropin (pST) Administration on Carcass Grades at a Major Commercial Packer

	Control/109 kg		PST/109 kg		pST/131 kg	
Commercial grades[a]	Number of pigs	(percent total	Number of pigs	(percent total)	Number of pigs	(percent total)
No. 1	80	(18)	117	(41)	295	(69)
No. 2	115	(26)	83	(29)	76	(18)
No. 3	142	(32)	65	(23)	39	(9)
No, 4	76	(17)	15	(5)	11	(3)
No. 5	34	(8)	2	(1)	4	(1)
Total	447		282		425	

[a]Commercial packer grades based on live weight and tenth rib backfat thickness:

No. 1 = 0.80 in. **or less (95-113 kg); 1.00 in. or less (1 14–122 kg); 1.20 in. or less (123 kg and up)**
No. 2 = 0.81-1.00 in. (95-113 kg); 1.01-1.20 in. (1 14-122 kg); 1.21-1.40 in. (123 kg and up)
No. 3 = 1.01–1.20 in. **(95-113 kg); 1.21–1.40 in. (1 14-122 kg); 1.41-1.60 in. (123 kg and up)**
No. 4 = 1.21-1.40 in. (95-113 kg); 1.41-1.60 in. (114-122 kg); 1.61-1.60 in. (123 kg and up)
No. 5 = Over 1.40 in. (95-113 kg); over 1.60 in. (114–122 kg); over 1.80 in. (123 kg and up)
NOTE: Percents may not add to 100 because of rounding.

SOURCE: K. Prusa et al., "Influence of Porcine Somatotropin (PST) on Carcass Characteristics of Pigs—A Summary of 15 Producer Trials," *Journal of Animal Science 69:344, 1991.*

backfat thickness, and increases the carcass percent lean and the weight of the major boneless pork cuts. Carcass dressing percentage increases with beta-agonist use, but decreases with pST administration. Both growth promotants show promise as methods to produce leaner pork cuts more efficiently. These changes have implications for present pork carcass grading and payment systems.

Potential Parameters for Alternative Grading System

USDA grades and grading criteria are rapidly becoming irrelevant for at least two reasons. First, the industry does not use USDA grades because they do not measure characteristics deemed important by industry. Second, advancing technologies, such as pST, will significantly change the composition of pork cuts to leaner products desired by consumers. Current USDA grading criteria based on backfat thickness and degree of muscling will not be relevant since there will be little, if any, difference in these characteristics among products produced with the new technology. For a grading system to be useful new criteria will be needed.

In determining potential criteria for use in alternative grading systems, it seems logical to focus on those characteristics considered most important by the ultimate consumer of pork products, with some consideration of the intermediate customer and the pork processor. The goal of an evaluation scheme as it pertains to pork quality is to predict from characteristics of fresh meat the general merit and value of the cooked product. In purchasing high-value products, consumers will consider price as well as such product characteristics as amount of lean versus fat and bone in the pork product; cholesterol levels; flavor, tenderness, texture, and firmness; degree of marbling; **juiciness;** color of the lean and fat; and aroma of the product. Moisture holding capacity is important for products to be cured or smoked.

External Fat

Both USDA and packer grades of pork are influenced largely by the amount of subcutaneous (external) fat, which accounts for approximately 70 percent of total carcass fat (8). Until recently, external fat was trimmed to approximately ¼ inch on pork cuts at the retail level. The Pork Market Basket Study completed in 1990 at the University of Wisconsin revealed that pork currently is trimmed to an average of only 1/8 in. of external fat.

Although trimming away undesirable external fat is one method of improving product quality and increasing consumer appeal, it is less appealing to the retailer who suffers the trim loss. Fat is perhaps viewed even less favorably by the producer who stood the consequences of inefficient gains of his animals (fat requires more calories than lean). Furthermore, carcasses with excessive external fat are likely to contain more intermuscular or seam fat, which is difficult to locate and remove, particularly in large roasts. Intermuscular or seam fat levels in excess of 20 percent are common in pigs; on average that type of fat represents 15 percent of carcass weight. Thus, trimming away of external fat deposits is a less than satisfactory solution to the fatness issue.

Photo credit: John Forrest, Purdue University

Grades for pork carcasses are based on a combination of subjective visual appearance and measurement of fat thickness (by simple ruler) and carcass weight. Fat thickness will not be a relevant criteria in the future.

Lean-Fat Ratios

An accurate method of determining directly the total fat percentage or lean-fat ratio of carcass products would be valuable for both consumers and packers. Present measurement procedures will be described in a later section. These techniques do not adapt well to the modern-

day rapid slaughter line. The Anyl-Ray procedure for assessing fat content of ground fresh meat samples is widely used in meat processing and has a relatively high degree of accuracy; however, it cannot assess fat content of the intact carcass.

Intramuscular Fat

The relative importance of marbling (intramuscular fat) to product acceptability is not clearly established. Malphrus et al., (34) reported a closer relationship between marbling and juiciness than between marbling and tenderness, although both exhibit a positive relationship. Further, marbling seems to be more important to palatability in fresh than cured pork and more important in chops than in pork roasts. However, marbling or intramuscular fat generally is considered a factor affecting palatability (7, 11, 53).

Cholesterol and Unsaturated Fatty Acids

Reduction of caloric content (fat content) of meat can contribute to reduction of obesity in humans and possibly improved health. The fat component of meat (particularly saturated fatty acids and cholesterol content) has been implicated in cardiovascular disease (23). More recently, red meat consumption has been linked to higher rates of colon cancer.

Muscle Quality

Problems of poor muscle quality continue to plague the pork industry. Pale, soft, and exudative (PSE) and dark, firm, and dry (DFD) muscle have been reported for 3 to 25 percent of carcasses in U.S. packing plants. Exudative pork has the tendency to lose water. It is important to monitor this problem if our foreign markets (particularly that of color-conscious Japan) and our domestic market are to be maintained or expanded.

Tenderness

Objective muscle shear measurements such as the Warner-Bratzler shear have been positively correlated with palatability (tenderness) of cooked pork as well as other meats (7). While there may not be a practical approach to obtaining this measurement on fresh carcasses, there may be a need to include some measure of tenderness in the grading process. In Denmark, shear force values have increased significantly with reduction in backfat and increased lean content. These changes have been significantly associated with a reduction in intramuscular fat. To date, there is no practical direct method of evaluating tenderness in fresh meat or in the meat animal carcass. Indirect indicators of meat tenderness such as color and texture of lean are questionable, at best.

Nutrient Content

Nutrient content variation in pork cuts with a similar lean-fat ratio primarily reflects the PSE condition and the extent to which nutrient-containing juices are exuded. For example, many nutritional elements are water soluble and may be lost during retail storage or cooking. Meyer et al. (37) examined B vitamin content and found greater losses from PSE muscle than from normal muscle. Niacin, however, was found to be higher in the final cooked PSE muscle. Biochemical differences in muscle metabolism were postulated as the reason for these differences. Collection and analysis of the drip from normal and PSE chops showed losses of protein, potassium, calcium, and magnesium per unit weight of lean were higher in PSE chops (16). Nutrient concentration of the drip was similar for the PSE and normal chops, but twice as much drip from PSE chops meant greater nutrient losses from the PSE product. Such losses, however, represent a very small portion of total nutrients present in a pork chop, and the differences observed did not appreciably change the nutritive value of PSE chops.

Flavor

Flavor is the most difficult to define of all the sensory traits. The lipid composition and metabolism of fat primarily are responsible for flavor (56). However, lean is also known to have important flavor components (9). Minimum quantities of fat necessary for "typical" flavor are not clearly defined, perhaps because juiciness becomes a palatability factor at low fat levels before loss of flavor occurs. The lipid component of pork can lead to the development of off-flavors. The high degree of unsaturated fatty acids in pork fat is the major reason for the potentially greater rancidity of pork relative to beef. There are no commercially feasible technologies currently available for measuring flavor. The primary technique utilized presently is sensory panels.

Options for an Improved Grading System

There are a number of alternatives to the current USDA pork grading system that warrant consideration. A few observations about the current situation and imminent changes in the pork industry will lay the background for consideration of possible changes in the pork grading systems. The current USDA pork grading system is not effectively differentiating between carcasses that vary widely in value. Packers are not currently using the USDA grading system for evaluating or pricing hogs. The packer

grading systems in use vary in the extent to which they differ from the USDA system. The inadequacy of the USDA grading system will become more apparent as producers begin using new growth promotant technology such as pST or beta-agonists.

Product characteristics valued by the consumer are only partially reflected in current grading systems. Fat content of pork products is a key factor for consumers, and external backfat thickness is a key factor in current packer and USDA grading systems. Fat content is related to calorie content, so calories are indirectly considered. While there currently are no grades for retail pork products, the labeling systems on a limited number of branded, processed products listing percent fat-free and calories serve the same purpose. Cholesterol and saturated fatty acid content, and muscle quality traits (color, tenderness, texture, etc.) considered important by consumers are not reflected in current grading systems. Technologies to measure these variables are not curently available or cannot be economically incorporated into the fast line speeds, etc., of the modem packing plant. (See box 14-A.)

Ideally, grading systems should provide recognizable homogeneous groups of products based on highly valued consumer characteristics that are accurately and efficiently measured. This would facilitate better informed purchasing and pricing decisions, and market feedback. Making producers and processors aware of value differences via the grading and pricing and market information system should improve industry resource allocation.

New growth promotants being developed for use in pork production are likely to change the compositional relationships within the pork carcass and the resulting consumer products. These changes will primarily impact lean/fat/bone relationships rather than sensory properties or eating quality. The compositional changes will necessitate further adjustments in current grading systems to provide accurate grading, equitable pricing, and accurate price reporting of pigs and their products or the elimination of grades altogether.

Several changes in the grading system that might improve industry performance are considered. Potential benefits and costs to consumers and industry participants are briefly analyzed.

Option l—Status Quo

Maintain the status quo in the USDA grading system, with a single measurement of backfat depth as the primary indicator of grade. This would be the least expensive alternative for the government and pork industry. Since packers currently do not use the USDA grading system, the impact on industry performance would be limited to the market information system that relies on USDA grades for price reporting. The Federal-State market price information based on USDA grades will become gradually less discriminating and useful, as an increased proportion of carcasses varying widely in value would be graded U.S. No. 1. The Federal-State Market News service has already deviated from using the USDA grading system by splitting their U.S. No. 1 grade carcass price reports into separate price reports for hogs with less than 0.8 inches of backfat and more than 0.8 inches of backfat.

Use of growth promotants will further widen the current disparity and variability between carcass grade and carcass value, especially in the highest grade. Differences between packer grading standards and USDA grading standards will likely continue to widen if packers continue to adapt their grading and evaluation systems to the changing characteristics of the market hog population. Several different packer grading and evaluation systems will continue to coexist, with differences in method and accuracy of evaluation. Producers will continue to have difficulty comparing alternative packer price quotations based on different grading systems. This would primarily affect producers' abilities to assure getting the best price for their hogs, and would have a small impact on resource allocation decisions by pork producers. Grades will continue to offer no useful information on lean quality or fat content to consumers, but individual packer grades and pricing systems likely will continue to offer some incentives for leaner hogs. However, many packer grading systems may have to be changed to reflect more accurately the changes in carcass composition from pigs produced using new growth promotants. The USDA grades will be even less able to reflect relationships between value characteristics and value. At the extreme, USDA grades could be rendered highly ineffective.

Option 2—Develop Grades Based on Lean-Fat Composition and Quality

Develop pork grades designed to reflect lean-fat composition as well as product characteristics most highly valued by the consumer. Use these grades for consumer products as well as at the packer level. Such grades might distinguish product groups differing in eating quality (tenderness, texture, freedom from PSE, freedom from odor, and color) and composition (percent lean, calories per ounce, etc.). There could be a separate quality grade, or a minimum quality standard for each composition grade.

Box 14-A—Technology To Evaluate Pork *Carcasses or* Procuts

Some 50 years of research and development has gone into the grading and classification of pig carcasses. Along with visual assessment and direct measurement of various fat and lean parameters with grids and metal rulers, the industry now has several highly sophisticated electronic techniques with which to measure economically Important characteristics of pork carcasses or products. Some of these await only the final stages of development before they can be applied commercially.

Current Technology Available for Measuring Composition of Pork Carcasses and Pork Products

Subjective Visual Assessment and Ruler/Grid Measurements

Currently, grades for pork carcasses are based on a combination of subjective visual appraisal of muscle thickness and objective measurements of fat thickness and carcass weight. In reality, most carcasses that are graded are subjectively evaluated by trained personnel However, actual measurementt of fat thickness at some point on the midline of the split carcass often is done with a simple ruler. the correlation of 10th rib backfat depth with quantity of fat-free lean mass is generally low (-0.27), but the measure is much more highly correlated with percentage fat-free lean mass (-0.56) (42). Combining measurements of the cross-sectional area of the loin muscle at the 10th rib with measurement of fat depth at the 3/4 point over the loin muscle significantly improves the prediction of either fat-free lean mass or percentage fat-free lean mass.

Carcass and cut Dissection

The standard to which most techniques for carcass evaluation are compared is the complete dissection of at least one side of the carcass into lean, fat, bone, and skin followed by chemical analysis of the soft tissues to calculate either a fat-free lean mass or a fat-standardized lean mass. In many instances the major primal cuts (ham, loin, belly, shoulder) are dissected individuality in order to determine changes in composition within the carcass that could be due to breed, or the utilization of growth stimulants or repartitioning agents. This is not practical in current commercial slaughter plants.

Carcass and cut Grinding and chemical Analysis

Grinding of the whole side or entire carcass followed by chemical analysis is sometimes utilized to determine composition under research conditions. while this technique reduces the labor that would be required for full dissection, it is very costly because none of the tissues can be salvaged for human consumption. Another disadvantage of this technique is that the composition of the edible soft tissues and the skeletal structures cannot beseperately determined. Like carcass and cut dissecttion, this too is not practical for commercial slaughter plants.

Photo credit John Forrest, Purdue University

The Fat-0-Meter is an optical probe that directly senses reflected light to determine tissue boundaries.

Optical and Mechanical Fat-Lean Probes

The Hennessy Grading Probe, Fat-o-Meter, Anatech PG-1OO, and Tecpro PG-200 are optical probes that directly sense reflected light to determine tissue boundaries. Accuracy levels of the grading probes in predicting percentage lean vary depending on the probe sites and combinations of parameters.

Mechanical-Pneumatic Assessmentt of Confirmation

An electro-pneumatic mechanical system measures the width of hams and loin. These measurements are combined with fat depth determined on the midline. This system is considerably more complex and expensive than an optical probe.

Potent/a/ Technology for Measuring Composition of Pork Carcasses and Pork Products

Magnetic Resonance Imaging and Nuclear Magnetic Resonace Spectroscopy

Magnetic resonance imaging (MRI) utilizes electromagnetic signals induced by a strong magnetic field to map and image fat and lean tissues. This technology is currently very expensive to purchase ($225,000 or more) and requires special shielding. It is slow and not currently adaptable to modem day slaughter plants. The high correlations with lipid (0.965), water (0.995) and protein (0.995) content from MR spectroscopy and the high resolution obtained from MRI images suggest that this technology could be used in research to replace time consuming and expensive carcass dissection. **To be effective in commercial application, further research and development to reduce the cost and increase the speed of operation would be required.**

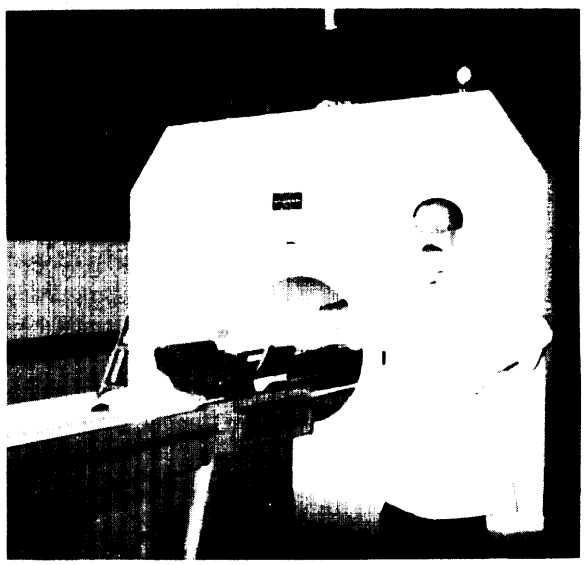


Photo credit: John Freest, Purdue University

Magnetic Resonance Imaging is a potential technology for measuring pork carcass composition by **using electromagnetic signals to map and image** fat and lean tissue.

x-ray computed Tomography

CAT scan or X-ray Computed Tomography produces a two-dimensional cross-sectional image of the carcass. A CAT scan of live animals has been shown to give highly accurate predictions of pork carcass composition without significant biases with respect to gender, breed, or live weight (55). The Norwegian Meat Marketing Board plans to use this technology to replace carcass dissection **in the validation of other** live animal and carcass grading instruments. High cost and the slow rate of data capture make this technology currently impractical for consideration **in online applications.**

Video Image Analysis of Conformation and Fat Depth

Video image analysis offers the possibility of objectively measuring the shape and thickness of pork carcasses, and could be combined with lean-fat probe data to improve predictive accuracy. In Denmark, a classification center has been developed for beef carcasses that uses video image analysis combined with an optical probe system. Tecpro, a company in Germany, is developing a similar system for pork carcasses. Costs for this system are difficult to determine at this point. Speed of operation should be limited only by computer capability for image processing.

Bioimpedance Analysis

Bioimpedance analysis (BIA) exploits the conductivity differential between the fat-free mass and fat to measure carcass fatness. As carcass fatness increases, the impedance to the flow of electricity increases. BIA has been shown highly accurate in predicting the fat-free soft tissue content of lamb caresses (27). Swantek and coworkers (61) reported that BIA accounted for 64 percent of the variation in fat-free mass in chilled pork carcasses. This system, as currently structured, would be difficlt to use in the context of current line speeds of many packing plants.

Ultrasound

Real-time ultrasonic imaging devices have the ability to produce cross-sectional images at various locations in either the live animal or carcass. An **image of the cross-section of the loin at the 10th rib can be used to obtain measurements of fat depth and loin muscle area. From this a model can be developed to estimate either the weight or percentage fat standardized lean mass. This technique may be useful in evaluating composition of seedstock animals or for evaluation of market animals to determine optimal market weight. With proper engineering and adaptation, ultrasound also may be useful in evaluating carcasses on the slaughter line.**

SOURCE: Office of Technology Assessment, 1992.

Including eating quality characteristics as grading criteria could make the pork grading system more useful at the consumer level. Unfortunately, few such characteristics are amenable to reasonably accurate and efficient measurement under commercial conditions. And it is not clear what quality measures would reflect characteristics consumers consider important but cannot visually evaluate themselves.

The cost and difficulty of implementing composition or quality grades beyond percent lean in ground pork might be particularly oppressive for small processors or retailers who do a small amount of meat processing. Mandatory label or grade information thus could have some undesirable structural implications. On the other hand, providing that information could level the playing field between small processors and larger retailers and processors with advertised brands. Further, reducing consumer uncertainty regarding any important quality characteristics by having a grade carry through to the consumer level could enhance consumer demand for pork products, and provide signals regarding undesirable quality to hog producers and pork merchandisers, which could stimulate quality improvements.

The technical feasibility of quality grading is a critical issue. Without a clear, pressing quality problem adversely affecting domestic or export demand, the potential benefits may not be large enough to justify this option even if the technical problems could be overcome. The price reporting system necessarily would become more complex as quality and composition differences would have to be reflected in price reports, requiring significant administrative costs and education of marketing system participants.

Option 3—Require Standardized Grading and Measurement Systems

Require packers to use standardized grading systems and a standardized effective measurement technology. Use that system for market price reporting.

This would be unpalatable for packers who usually are extremely independent and negative toward more government intervention in their operations. Standardized grading systems would make price reporting easier and more accurate, and facilitate comparisons of grade-related packer bids or hog prices for producers. However, this approach would not allow individual packers to adjust to any special considerations relevant to their customers or suppliers. Moreover, USDA grading systems have been notoriously slow to change when conditions warranted it, and the same might be true of any standard grading system. Small packers may find it difficult to compete if needed changes are expensive to implement.

Greater equity among producers may be facilitated by these changes. Other economic benefits are in the form of faster industry adjustment to consumer wishes and improved resource allocation and efficiency in the long run. The costs would be incurred in the short run, primarily by packers (especially small packers) and producers of "poor quality" hogs. Establishing a mandatory system would involve significant research and development costs by the USDA and packers (and subsequent processors and merchandisers of pork products if the quality and composition grades would be carried through to the consumer level). The added operating costs could also be significant. Standardization across all packers and merchandisers would certainly improve the accuracy and ease of acquiring price reports related to the USDA grading system, but the complexity of the system would also be increased significantly.

Option 4—Use Percent Lean as USDA Grade Criteria

More extensive use of lean-fat probes to predict carcass lean percent suggests that percent lean (based on loin muscle depth and backfat thickness, off-midline) rather than the current percent-lean cuts (primarily based on midline backfat thickness) is a grading criterion more in tune with the measurement technology becoming dominant in the pork industry. If the USDA simply based grades on percent lean without tying particular backfat or loin depth measures to any numerical grades (e. g., 52 to 53 percent lean rather than U.S. No. 1) the grade relationships would be less apt to lag behind changes in the hog population.

The percent-lean measure, which is the common standard for carcass evaluation by meat scientists today, has one flaw. It does not reflect the fact that lean from a loin or ham has a different market value than lean from another part of the animal. If the hog population has significant variability in the proportion of carcass lean coming from various parts of the animal, those differences in value would not be accounted for in a grading and pricing system based on (total) percent lean.

However, this system might be superior in value discrimination to some packer systems now in use, and would be compatible with the probe technology currently used by several large packers. Further, the percent-lean criterion at the carcass level would be consistent with the lean-fat composition information that many consumers demand for pork products.

Significant administrative costs would be required to establish new grades and to implement the price reporting system. Price reporting might be difficult for packers not using probes, but current measurement systems could be adapted to the percent-lean criterion. If slightly less accuracy in grade reporting is acceptable, it probably would not be necessary to require use of probes for this system to be workable. If probes were required, this would involve significant transition costs for many packers.

Option 5—Abolish the USDA Pork Grading System, and Use Percent-Lean Descriptive Terms for Classes of Market Hogs in Government Price Reporting

Currently, the USDA grading system is used only by the Federal-State Market News Service in providing the market classes for price reporters to use. Many packers already are using the percent carcass lean as their basis for market hog grading and evaluation; others have not adopted that system, often because of perceived problems with the probe measurement system or because their own system is considered adequate. Asking packers to shift to a new USDA grading system would involve significant transition costs to packers not using a percent-lean probe system, and more market costs for packers currently using those systems. If packers do not use USDA grades now in their grading and evaluating systems, a high likelihood exists that they would continue to use their own systems, which they have tailored to their specific needs, even if the USDA system was improved. In addition, USDA grades require significant time and administrative costs to promulgate, and may in the future lag behind practices used in the industry. These costs can be avoided by eliminating official grades. Instead, prevalent industry terminology (weight and percent-lean classes) could be used to report prices by government price reporting agencies, in consultation with the users of the price reports. This could be done with much less administrative cost, and retain greater flexibility to change with industry practices and technology. Since many hog producers may not be familiar with the percent-lean terminology, price reporters could use percent-lean ranges *and* corresponding backfat ranges with which farmers are familiar in price reporting for a transition period.

The benefits of this system would be the lower cost and greater adaptability to changes in the market hog population and measurement technologies, due to reduced bureaucracy involvement; and a better basis for government price reporting. It would encourage the movement by many packers to have their prices more accurately reflect carcass merit. The costs would include those necessary for government agencies to develop comparable percent-lean and backfat measurements for use in translating prices paid on the basis of nonconforming grading systems into prices for the percent-lean equivalent classes. Also, the lack of uniformity of packer grading and evaluation systems would continue, with attendant problems for producers in comparing packer bids based on different systems. However, the increased use of percent-lean systems should gradually lead to easier comparisons.

Conclusions

Many packers are shifting to probe measurement systems where their grades and prices are based on estimates of carcass lean percentages. Since these estimates are not based solely on backfat, the USDA could shift to carcass lean percentage as the basis for both grade and price reporting. However, it does not seem likely that such a change will prompt many pork slaughter processors to adopt the USDA grading system, since many of them have their own system already developed and adapted to their needs. Moreover, changing internal evaluation systems is costly.

Grading or labeling the quality of lean would appear desirable in pork products and carcasses. However, this seems impractical at this time due to the absence of commercially feasible measurement technology. Nutrient composition or similar labeling of fat content, calories, fatty acid profiles, or cholesterol content for pork products at the consumer level would provide information that could enhance demand or provide clearer signals to producers and processors regarding consumer preferences. Some branded pork processors currently are providing some of this information. In addition, some industry consumer information programs are beginning to move in this direction. Unfortunately, the commercially available technology for meat-quality evaluation is primarily adaptable to ground meat, and fat content is more easily measured than some other characteristics. Adapting this approach to highly variable intact fresh and processed pork products could add relatively significant capital and labor costs, especially in small processing and merchandising operations. If effective quality measurement technology were developed, the quality measurements and information provided would need to be incorporated into product evaluation and pricing throughout the marketing system. Then, consumer reactions to differences in quality would be effectively transmitted through the system and affect prices paid to producers.

Several promising technologies that might provide accurate estimates of lean/fat composition of carcasses or

pork products, including products affected by the new growth promotants, are in the research and development stage. This research could be encouraged. These technologies, when commercially feasible, could be incorporated with grading programs that focus on carcass percent lean. Classifying pork carcasses via carcass lean percentages could be initiated with the view toward adding lean-quality information at a later date. When a commercially feasible lean-quality measurement becomes available, pork carcass grades could be determined by carcass percentage lean and quality of the lean. Dramatic adjustments in reporting of pork prices would not be needed to incorporate quality information with carcass percent-lean information.

Finally, the descriptive terms (currently primarily USDA grades) used in government price reporting could be changed to percent-lean classes, with related backfat measures reported for a transition period. In the longer term, quality information can be added when commercially feasible. When fully implemented, price would be reported by percent-lean and lean-quality classes or measurements. If there is a need for a USDA grading system, it could be based on carcass percent lean, measurements (not grades), with lean-quality information added when it becomes commercially feasible to do so. However, packers are unlikely to use an improved voluntary system. Price reporting agencies should be able to adopt percent-lean ranges for reporting prices with less bureaucratic cost and more flexibility than would be the case for changes of grading systems. Consequently, a strong argument can be made for abolishing the USDA pork grading system. This is essentially what has been happening de-facto in the pork industry over the last decade.

THE FRUIT AND VEGETABLE GRADING SYSTEM[2]

The U.S. Department of Agriculture has a long-established system for fruit and vegetable grades. Standards used to determine a grade include "attributes," such as size, quality, and condition, and their related "tolerances. " For example, one attribute for fresh market potatoes is "free from sunscald. " The tolerance for this attribute is "no more than 10 percent defects at the point of shipping. " This attribute and its tolerance are used along with other attributes and tolerances to designate grade. Attributes are based on sensory characteristics, such as touch, sight, and taste, as well as shelf-life considerations, palatability considerations, or some combination of these factors.

Challenges have been raised to the Federal grading system. Some question grades that do not explicitly include health and nutritional factors. Others argue that the current sensory-based grade attributes indirectly encourage the use of chemicals in production, so as to minimize blemishes and ensure vibrant skin-color.

Consumers are increasingly concerned about the use of chemicals or chemically based ingredients in the production and preservation of our food supply, both for environmental and health reasons. There is concern that chemicals used in the production process may damage the environment and that chemical ingredients in or on food may impair human health, perhaps in ways yet unknown to the scientific community.

Consumers increasingly want to be more fully informed about choices available in the marketplace. Given such information consumers will, through their purchases, indicate levels of nutrition they want, what levels of pesticide residue they are willing to tolerate, and what level of blemishes they are willing to accept.

Thus, some alternative or revised set of grade attributes might be more socially desirable than current sensory-based attributes. The natural question that arises is whether it is more feasible and desirable to incorporate additional or modified attributes, such as nutrition information or other "nonsensory" information, into current standards; or to identify conceptual alternatives to the current sensory-based standards. This case study focuses on the use of sensory and potential alternative grading attributes for fruits and vegetables.

Fruit and Vegetable Production and Consumption

The U.S. fruit and vegetable industry accounts for 8.7 percent of the market value of all agricultural products sold in the United States (table 14-5). Fruits, nuts, and berries account for 5.2 percent of the market value whereas vegetables account for 3.5 percent of the market value. Reflecting their high market value per acre of production, fruits, nuts, berries, and vegetables account for only 1.8 percent of total U.S. acreage.

[2]This analysis is based on the OTA commissioned paper "Assessing Federat Grade Criteria for Fruits and Vegetables, " by Thomas Sporleder, Rebecca Boerger, Mark Bennett, James Hoskins, Eugene Jones, Timothy Rhodus, Kurt Wiese, and Carl Zulauf, all associated with the Ohio State University (59).

Table 14-5—Market Value of Agricultural Products Sold and Total Acreage, United States, 1987

	U.S. total	Total fruits, nuts and berries	% of total	Vegetables	% of total
Market value of agricultural products sold ($1 ,000)	136,048,516	7,084,818	5.2	4,698,083	3.5
Acreage (acres)	282,223,880	4,404,946	1.56	3,467,563	1.23

SOURCES: 1987 Census *of Agriculture AC87-A-51,* **U.S. Department of Commerce, Bureau of the Census, November 1989 and** *Fruits and Nuts Situation and Outlook Report Yearbook,* **U.S. Department of Agriculture, Economic Research Service, Washington, DC, November 1990,**

Table 14-8-Top 12 Commercial Shipping Point Commodities, Fresh Inspected Shipments, Fiscal Year 1990
(Reported in cwt.)[a]

Commodity	Tonnage
Potatoes	100,805,477
Tomatoes	25,645,867
Apples	19,313,891
Onions	15,667,916
Grapefruit	13,628,587
Grapes	9,166,998
Oranges	7,976,860
Cantaloupes	7,483,463
Pears	6,790,235
Lettuce	6,751,039
Peaches	6,071,965
Plums	5,179,140

[a]**Inspected fresh product only.**

SOURCE: Fresh Products Branch, Annual *Report for Fiscal Year 1990,* **AMS, U.S. Department of Agriculture, Washington, DC, 1990, and "Fruit and Vegetable Shipments:Market News, AMS, USDA.**

Table 14-7—Number and Type of USDA Grades for Fruits and Vegetables

Category	Number of grade standards
Fruits for fresh market:	
Wholesale market	29
Raw products for processing	15
Fruits **for processing**	15
Canned fruits	36
Dried and dehydrated fruit ,	14
Frozen fruits ,	21
Vegetables for fresh market:	
Wholesale market	**58**
Consumer retail market	**12**
Vegetables for processing	**24**
Canned vegetables	**39**
Frozen vegetable	**26**

SOURCE: U.S. Department of Agriculture, Agricultural Marketing Service

In terms of tonnage at commercial shipping points, the most significant commodity among fruits and vegetables for fiscal year 1990 was potatoes (table 14-6). Tomatoes were second in volume but with only about one-fourth the volume of potatoes. Apples were the third largest commodity volume-wise with about three-fourths the volume of tomatoes.

Apples, oranges, potatoes, and tomatoes were chosen here for specific case analysis. These commodities were selected because they represent a wide variety of grade standards, have relatively high per capita consumption, and figure significantly in today's food markets. Annual value of production for these commodities ranges from $1 billion for apples to nearly $3 billion for potatoes. Annual consumption per capita for the four commodities ranges from about 15 pounds for oranges to over 127 pounds for potatoes. Since 1970, per capita consumption of all fruits and vegetables in the United States has trended upward.

USDA Grade Standards

Current grade standards for fruits and vegetables are administered by the U.S. Department of Agriculture (USDA) under authority of *The Agricultural Marketing Act of 1946.* The purpose of these sensory-based grade standards is to encourage uniformity and consistency in commercial practices related to the quality, quantity, and condition of agricultural products shipped in interstate commerce.

Use of USDA grade standards is voluntary. However, if a firm decides to use grade standards and designate the U.S. grade on a package label, they must use USDA's grade standards.

Fruit and vegetable USDA standards can be grouped into categories (table 14-7). Most grade standards for fresh fruit and vegetables pre-date 1960. Grade standards for processed fruit and vegetables generally are of more recent vintage.

At the commercial shipping point nearly 90 percent of fresh potatoes and approximately 77 percent of fresh

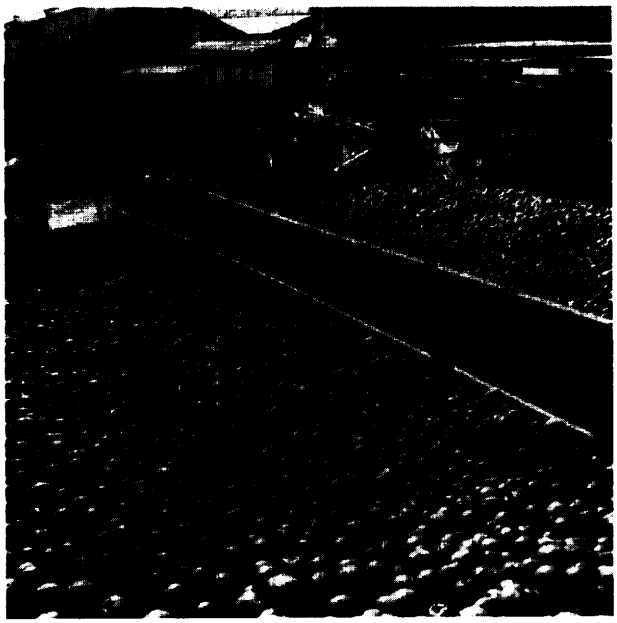


Photo credit: Grant Heilman, Inc.

Voluntary sensory-based grades encourage uniformity and consistence of agricultural products. At least 75 percent of fresh tomatoes are graded.

tomatoes are graded. Only about one-third of fresh apples and around one-fifth of the fresh oranges are graded.

At the raw product processing stage, nearly 80 percent of potatoes were graded while only about 5 percent of the tomatoes were graded. Approximately 86 percent of the oranges and nearly 30 percent of apples are graded.

Grading attributes can be broadly divided into three categories: size, quality, and condition. Size of a commodity can be described by diameter, length, weight, and uniformity (65). Quality factors are defined as "the combination of the inherent properties or attributes of a product which determines its relative degree of excellence" (26). In general, quality factors refer to the attributes of a commodity that remain permanent once the commodity is harvested. Examples include variety, cleanliness, shape, and maturity. Defects in quality can be divided into four classes:

1. fungal injuries,
2. insect injuries,
3. mechanical injuries, and
4. other defects (ill shaped, undesirable color, sunburn, growth cracks, and dirt) (65).

Condition refers to

> the relative degree of soundness of a product that may affect its merchantability and includes those factors that are subject to change after harvest. Condition (i.e., ripeness or freshness) may reflect age, improper handling, storage or lack of refrigeration. . . . (10).

Along with attributes, tolerances are used to determine grade. Tolerances are legal limits of acceptable size, quality, and condition attributes. They generally are stated in percentage terms, and can vary by product, use, or size of the individually packaged product. The tolerances for U.S. No. 1 apples illustrate the variety of forms that tolerances can take:

1. no more than 10 percent of apples with quality and condition defects including no more than 2 percent of apples with decay, 2 percent with internal breakdown and 5 percent with wormholes; and
2. the apples cannot be further advanced in maturity than generally firm ripe.

Size, quality, and condition attributes, as well as tolerances, differ for different commodities, they also vary with market destination. In general, attributes and tolerances are more strict for fresh produce destined for the fresh market than for fresh produce destined for the processing market. For example, U.S. Extra No. 1 fresh potatoes at the wholesale level must be firm, a condition attribute. In contrast, U.S. No. 1 potatoes for processing at the wholesale level have a comparable condition attribute of moderately firm. Similarly, the retail consumer grade for fresh produce tends to be more strict than the wholesale standard, To illustrate, for U.S. No, 1 tomatoes at the wholesale level, defects can total no more than 10 percent at shipping points or no more than 15 percent en route or at the destination point. On the other hand, defects can total no more than 5 percent for U.S. Grade A fresh tomatoes at the consumer retail level.

Most sensory attributes are measured by inspectors using their sense of touch, sight, and smell. Many technologies, however, have been developed to measure sensory attributes of foods. A considerable amount of automation and computerization is occurring in this area. For example, up-to-date mechanical harvesters used in the harvest of processing tomatoes are computer equipped and give a preliminary objective color assessment that is more accurate than previous human, subjective evaluation. Advancements in computer technology are leading to fully automated color and size measurements that will permit accurate sensory evaluation of products from the field to the retail store, with perhaps the need for only limited human spot-checking (38). One large fruit pack-

Photo credit: Grant Heilman, Inc.

Most sensory attributes are measured by inspectors using their sense of touch, sight, and smell. Inspectors grade nearly 90 percent of all fresh potatoes.

ing house in Florida recently added computerized equipment that weighed, optically scanned for dimensions, and used an infrared camera to determine fruit size. Used together, the processes are able to determine density and cull fruit that is internally damaged by freezing (63).

Conceptual Considerations of Grade Standards

A grade is assigned to fruits and vegetables by applying prespecified standards to a random sample of the commodity being graded. Three conditions must be met for an attribute to serve as a grade standard. First, the quality, condition, and size attributes stated in the standards must be observable or measurable. If an attribute cannot be observed or measured, then it is not possible to include it in a grading standard. Second, information about the attribute must exist and be available to the public.

Third, the attribute must vary among individual specimens of the commodity. If the attribute does not vary, then including it in the grading standard would provide no information. The use of tolerances on quality, condition, and size attributes reflects this variability. Tolerances allow for a sample to obtain a given grade even though not all specimens in the sample have the same quality, condition, and size attributes.

Basing grades on the presence and quantity of chemical residues and nutrient value, for example, mandates knowledge about chemical residues and nutrient values. If these two attributes vary among samples of a commodity, and are measurable, they can be incorporated into or substituted for existing grade standards. The next two sections address the measurement and variability of nutrient and chemical residue attributes in fruits and vegetables. Their purpose is to introduce the conceptual basis for two different fruit and vegetable grade standards—one based on nutritional content, the other on chemical residues.

Nutritional Attribute Measurement

Cost-effective techniques that provide information on a timely basis do exist for several nutrients (box 14-B). The willingness of consumers to pay for this information could broaden the range of cost-effective techniques for nutrient analysis. An alternative approach is to determine if sensory characteristics also convey information about nutritional characteristics. In other words, can sensory grade attributes be used to evaluate the nutritional characteristics of fruits and vegetables? This question is addressed in the next section.

Nutritional Attriutes Variation

Knowledge Gaps

While much is known about the nutritional value of fruits and vegetables, inadequate data exist in many key areas **(3).** (See tables 14-8 and 14-9.) Little or no data exist for 9 nutritional components of fresh fruits, 14 nutritional components of frozen or canned fruits, 18 nutritional components of fresh vegetables, and 12 nutritional components of frozen and canned vegetables. This lack of information is due in part to the minute quantities of some nutritional components of fruits and vegetables, and uncertainty as to the exact nature of these components' contribution to human nutrition. For example, the fat soluble vitamins (A,D,E, and K) can be accurately assayed and quantified in most samples. However, quantities of these vitamins may be present in bound form or other forms not utilizable or under-utilized in human physiological processes. Thus, their overall role in human nutrition is uncertain. Additional research on nutrition of fruits and vegetables is needed before all nutritional attributes can be included in a grading standard.

B0X 14-B-Technology for Nutrient Attribute Measurement of Fruits and Vegetables

Nutritional attribute of food in general cannot directly be sensed by consumers. Consequently, scientific methods **and instruments are needed to measure these attributes. Currently available methods and instruments are numerous and sophisticated.**

Currrent Methods for Determining Nutrient Content

In addition to water, fruits and vegetables usually contain significant amounts of most or all types of carbohydrates, such as sugars, starches, and fiber. They also contain vitamins (notably vitamins A and C) and smaller, but nutritionally significant, amounts of minerals and protein. Specific methods of analysis exist for each nutrient category. These methods have varying degrees of accuracy, simplicity, and cost.

For carbohydrates, analytical methods indclude observing color changes, microbial assays, enzymatic assays, and chromatography. Chemical extraction procedures will use one of these methods to extract and differentiate simple sugars, complex sugars, starch, and dietary fiber for analysis. A technique recently developed for quantifying fiber is enzymatic degradation.

Protein composition generally is determined by empirical techniques. Proteins are decomposed into constituent amino acids by hydrolysis (a decomposition procedure using water). These amino acids are isolated by chromatography (a technical procedure that separates substances based on factors of size, electrical charge, or affinity for another compound).

Analysis of mineral components **in plants is challenging because minerals generally are present only in minute quantities. Traditionally, quantification of mineral has involved analysis of the inorganic ash residue obtained from burning a plant sample. Mineral ash from fresh fruits ranges from 0.2 to 0.8 percent of the weight of the entire fruit, and the quantity of ash generally is inversely related to moisture content. Mineral content in vegetables is usually higher, at about 1 percent. The oldest analytical techniques applied to mineral ash forms of spectroscopy (xray fluorescence absorption.) Spectroscopy is the observation and measurement of radiation emitted from chemical elements after their atoms have been excited in a certain way. Each element** has a characteristic pattern of wavelengths following excitation (45).

Assessment of *Current Techniques* and Methods

Beecher and Vanderslice have cattegorized methods of nutrient analysis based on their level of accuracy and other attributes as adequate, substantial, conflicting, and lacking. Their criterion for accuracy is the production of an

analytical value within 10 percent of a true value when a nutrient is presentn food at a nutritionally significant level, defined as greater than 5 percent of the Recommended Daily Allowance (RDA) per standard serving or daily intake, whichever is greater. Many methods fail to meet this criterion (45).

Adequate and "substantial" methods are highly accurate, Speedy, and modest in cost-defined as less than $100 per test. "Conflicting" and "lacking" methodologies are unlikely to render valid results **under conditions of routine analysis.**

Although problems exist with accurate assessment of nutritional **components of fresh fruits and vegetables, analysis of fresh produce is less Problematic than is analysis of processed foods. Adequate and substantial methods of analysis already exist for many nutrients in fresh fruits and vegetables.**

Developments in Nutrient CompositionMeasurement

Technological advances are improving the ability to accurately and expeditiously measure nutrient components. An example is flow injection chromatography (60). it permits numerous rapid sequential analyses and is appropriate for constituents other than proteins, including vitamins, and carbohydrates. Similarly, a new advance in spectroscopic analysis is Simultaneous Multielement Atomic Absorption Spectrometry (SIMAAC). It is a furnace atomization technique that compares analytic signals to known calibration standards. Simultaneous Muitielement Atomic Absorption Spectrometry, which permits simultaneous analysis ofup to **16 elements, has important implications for more rapid sample turnout in nutrient analysis of foods. However, careful sample preparation and accurate instrument calibration is required to avoid erroneous results (60).**

Other new techniques in food analysis Include use of bioindicators, mass spectroscopy, delayed light emission, xray diffraction, supercritical $C0_2$ chromatography, microbial assays, and computerization. Although the list is not all inclusive, it suggests some of the directions food analysis will follow. Last, advances in computer technology point toward further miniaturization of techniques as well as improved speed and accuracy.

SOURCE: Office of Technology Assessment, 1992.

Table 14-8-Knowledge of Nutrient Composition of Fresh Fruits

Nutritional component	Little or no data	Substantial data	Inadequate data	Not applicable
Individual sugars		x		
Starch	x			
Nutrient fiber			x	
Total fat		x		
Fatty acids			x	
Sterols			x	
Calcium		x		
Iron		x		
Phosphorous		x		
Sodium		x		
Magnesium		x		
Potassium		x		
Zinc		x		
Total protein		x		
Individual amino acids			x	
Folacin			x	
Vitamin D				
Vitamin E		x		
Biotin	X			
Choline			x	
Pantothenic acid			x	
Vitamin A		x		
Vitamin B1 (Thiamin)		x		
Vitamin B2 (Riboflavin)		x		
Vitamin B6		x		
Vitamin B12				x
Vitamin C		x		
Niacin		x		

Tables from: G.R. Beecher and J.T. Vanderslice, "Determinationof Nutrients in Foods: Factors That Must Be Considered," Modern *Methods of Food Analysis*, K. Stewart and J. Whitaker (eds.), 1984, pp. 34-41. Tables prepared from USDA, Nutrient Data Research Branch, Consumer Nutrition Division of the Human Nutrition Information Service research publications.

Variation in Nutrient Attributes

To ascertain whether the nutritional value of a fruit or vegetable varies among individual samples of the fruit or vegetable, relevant information for potatoes, tomatoes, apples, and oranges was collected by examining the past 10 years of International Food ScienceandTech*nology Abstracts.*

Nutritional variation was found to exist among samples of fruits and vegetables in several published studies. For example, protein, niacin, and thiamin increased in potatoes while ascorbic acid as well as starch decreased when nitrogen fertilizer was applied. Sandy soils increased the amounts of protein, ascorbic acid, riboflavin, niacin, sodium, and iron in potatoes but decreased the amounts of thiamine, magnesium, and calcium (2). One study (35) indicated that samples of a single potato cultvar may differ widely in sugar content after 9 weeks of storage. Incorporating phosphorus or potassium to the soil had no effect on protein or nonreducing sugars, but phosphorus increased the starch and sugar content of the potatoes.

Environmental factors influence the sugar-acid ratio, beta-carotene, and nitrogen content and quality of tomatoes (24). Nitrogen and potassium ratios also influence dry matter, soluble dry matter, and beta-carotene of fruits as well as their keeping quality. Maturity of the tomato affects total sugars and the ratio of reducing to nonreducing sugars as well as the percentage of total soluble solids. Mineral content and composition in tomatoes are influenced by location and growth but do not vary among cultivars. However, cultivar and fertilizer both affect the amount of ascorbic acid in tomatoes (25, 44).

In apples, seasonal variation affects anthocyanin, total phenol content, diameter and weight, total soluble acids, acidity, and Magnes-Taylor puncture values. Bruising and softening rates in cool storage varied by cultivar (13, 32).

Vitamin C in oranges was found to be influenced by variety, cultural practice, maturity, climate, fresh fruit handling, and processing factors such as packaging and storage. Percentage of juice, Brix, acidity, and total sugars varied with orange cultivar (40, 54).

In summary, the nutritive composition of fruits and vegetables varies due to factors of climate, geographical location, cultivar, soil variables, irrigation practices, fer-

Table 14-9—Knowledge of Nutrient Composition of Fresh Vegetables

Nutritional component	Little or no data	Substantial data	Inadequate data	Not applicable
Individual sugars			x	
Starch		x		
Nutrient fiber			x	
Total fat			x	
Fatty acids			x	
Cholesterol				**X**
Sterols			x	
Calcium			x	
Iron			x	
Phosphorous			x	
Sodium			x	
Magnesium			x	
Potassium 4			x	
Zinc		**X**		
Total protein		**X**		
Individual amino acids			x	
Folacin				**X**
Vitamin D.....			x	
Vitamin E			x	
Biotin	**X**			
Choline			x	
Pantothenic acid...	**X**			
Vitamin A....,..		x		
Vitamin B1 (Thiamin)		x		
Vitamin B2 (Riboflavin)		x		
Vitamin B6			x	
Vitamin B12, ...				x
Vitamin C..... 4		x		
Niacin		x		

Tables from: G.R. Beecher and J.T. Vanderslice, "Determination of Nutrients in Foods: Factors That Must Be Considered," *Modern Methods of Food Analysis*, K. Stewart and J. Whitaker (eds.), 1984, pp. 34-41. Tables prepared from USDA, Nutrient Data Research Branch, Consumer Nutrition Division of the Human Nutrition information Service research publications.

tilization practices, and seasonal and annual variation. Post-harvest physiology and handling introduces additional sources of variation in the nutritional composition of fruits and vegetables.

Conclusion

Available evidence suggests that intracommodity variation in nutritional value does exist. Thus, one requirement for developing a grade standard based on nutritional characteristics is fulfilled. However, the lack of adequate data on several nutritive components of fruits and vegetables remains a problem. This deficiency needs to be rectified before nutritive attributes can be included in grade standards incomprehensive manner.

Assessing the Relationship Between Nutrient and Sensory Characteristics

Concept

Whether it makes sense to change from sensory-based grading to nutrient-based grading depends on the extent to which nutrition and sensory characteristics are related. To illustrate, consider the extreme case. Suppose all criteria contained within the sensory characteristics base for grade standards were positively correlated at 1.0 with whatever criteria were chosen for nutrition-related grade standard. This would imply little or no impact from a change to an alternative base. Obviously, however, it is more likely that some (but not all) sensory criteria are correlated with some (but not all) nutrition-related criteria.

As discussed earlier, current grade criteria for fruits and vegetables are based on three main considerations—quality, condition, and size. In general, the quality criteria involve maturity, cleanness, shape and form, color, and quality defects. The condition criteria generally involve firmness, condition defects, and color.

A matrix relating current sensory grade criteria to nutritional characteristics is presented in table 14-10. The current grade standards, generalized across all fruits and vegetables, appear as rows in the table. The columns are various nutrition-related characteristics. Some

Table 14-10-A Method for Conceptualizing the Relationship Between Sensory Characteristics and Nutrition Characteristics

Current grade criteria, generalized across all fruits and vegetables	Conceptual nutrition-related characteristics								
	Vitamins	Minerals	Calories	Enzymes & proteins	Carbo-hydrates	Fats & oils	Sodium	Calcium	Fiber
Quality									
Maturity									
Cleanness									
Shape/Form									
Color									
Quality defects									
Fungus injury									
Insect injury									
Mechanical injury									
Other[b]									
Condition									
Firmness									
Condition defects									
Decay									
Bruising									
Freezing									
Discoloration									
Ground color/color									
Size									

[a]**The OSU study team believes that this list accurately portrays the criteria which predominate across all fruits and vegetables. However, there are some criteria in the current standards for a specific fruit or** vegetable not reflected in this list. Such omissions have scant consequence for the present assessment.
[b]**Other** is defined as ill-shaped, undesirable color, sunburn, growth cracks, and/or dirt.

SOURCE: Office of Technology Assessment, 1992.

cells of the matrix are not expected to be of equal relevance. For example, one might expect positive correlation between maturity and calories per gram, whereas the fiber-insect injury cell might not have any correlation or importance. Similarly, if a nutrition-related base for standards were ever adopted, one would not expect all the criteria listed as columns in the table to be included in a standard. At this point, however, there are no compelling reasons to exclude cells formed by the matrix from examination, except for the cells involving cleanness and shape and form. These two current sensory grade criteria are not related to nutrition attributes. Therefore, these two rows are shaded to indicate no correlation is expected.

Each of the 126 relevant cells of the matrix, in effect, defines a specific topic where knowledge is desired. A task of the assessment of the nutrition-related base for grade standards was to carefully review existing scientific literature for each of the relevant cells for the four commodities chosen for analysis—potatoes, tomatoes, apples, and oranges. The past 10 years of volumes of the *International Food Science and Technology Abstracts* have been examined for research literature relevant to the matrix and the case study commodities.

Current Information

A summary of the findings is presented in table 14-11. A letter for each of the investigated commodities (A for apples, O for oranges, P for potatoes, and T for tomatoes) is placed in a cell if information existed about the nutrition-sensory relationship.

As is evident from the summary table, no scientific literature was found for many of the cells. For only about 8 percent of the 504 total cells (126 for each commodity) does at least one research article exists. No studies were found that investigated the relationships between current sensory grade characteristics and sodium while only one study examined calories. The inevitable conclusion is that much is unknown about the relationship between sensory characteristics and nutrition-related characteristics.

Nonetheless, some knowledge is available. The relationships between maturity and nutrition, especially with respect to vitamin C and carbohydrates, are the most researched. The concentration of vitamin C increases with maturity in potatoes and tomatoes, but decreases dramatically in oranges and potatoes the longer these commodities are held in storage. Carbohydrates in apples and tomatoes are positively related to ma-

Table 14-1 l—Summary Table of Scientific Literature on the Relationship Between Sensory Characteristics and Nutrition Characteristics for the Four Study Commodities.

Current grade criteria, generalized across all fruits and vegetables	Conceptual nutrition-related characteristics								
	Vitamins	Minerals	Calories	Enzymes & proteins	Carbo-hydrates	Fats & oils	Sodium	Calcium	Fiber
Quality									
Maturity	A, O, P, T	A,O, P, T	T	o	A, O, P, T	O, T		A,O,T	A, T
Cleanness									
Shape/form									
Color									
Quality defects									
Fungus injury									
Insect injury									
Mechanical injury					P				
Other[c]									
Condition									
Firmness									A, T
Condition defects									
Decay	0				o			A	
Bruising	P								
Freezing	P, T				P	T			
Discoloration									
Ground colorl/color									
Size							P		

[a]**Key: A =** apples, O = oranges, P = potatoes, T = tomatoes
[b]% OSU study team believes that this list accurately portrays the criteria which predominate across all fruits and vegetables. However, there are some criteria in the current standards for specific fruit or vegetable not reflected in this list. Such omissions have scant consequence for the present assessment.
[c]**Other** is defined as ill-shaped, undesirable color, sunburn, growth cracks, and/or dirt.

SOURCE: Office of Technology Assessment, 1992.

turity. In potatoes, starch is more readily converted to sugars after harvest. Conversely, oranges show a decrease in glucose and fructose during storage and as they decay.[3]

Chemicals and the Grading System

Current Pesticide Usage in the United States[4]

Herbicides, insecticides, and fungicides comprise the three major components of the $4 billion-a-year U.S. agricultural pesticide market. Herbicides surpassed insecticides in the late 1960s to become the most utilized pesticide class. With $2.5 billion in sales, they accounted for 90 percent of the total pesticide pounds applied in 1986. The insecticide agriculture market was second with $1.0 billion in sales, followed by fungicides with sales of about $265 million.

In 1982, slightly more than 500 million pounds of pesticide active ingredients were utilized in American agriculture. Pounds of pesticide active ingredients were 170 percent higher than in 19&l, while acres under cultivation remained essentially constant. By 1987, pounds of active ingredients had declined to about 430 million pounds. Ninety percent of all herbicides and pesticides are applied to four crops: corn, cotton, soybeans, and wheat.

Fungicides account for about 10 percent of all pesticides applied in agriculture and are the most significant pesticide product used in production of fruits and vegetables. Insecticide use is also significant in fruit and vegetable production, however, its use has declined in recent years through the adoption of new, more effective products and innovative strategies such as crop rotations and Integrated Pest Management.

Most new pesticide products introduced since 1980 have been herbicides. Thirty-seven herbicides have been registered with the Environmental Protection Agency (EPA) since 1980 as compared to 10 fungicides. This

[3]Note that many of these articles address post-harvest changes. These changes are not a maturity issue; however, they do illustrate the importance of post-harvest storage and handling techniques to the nutritional value consumers ultimately derive from a stored fruit or vegetable.
[4]Information in this section comes from pages 43 through 49 of *Alternative Agriculture,* a report by the Committee on the Role of Alternative Farming Methods in Modem Production Agriculture, Board of Agriculture, National Research Council, 1989.

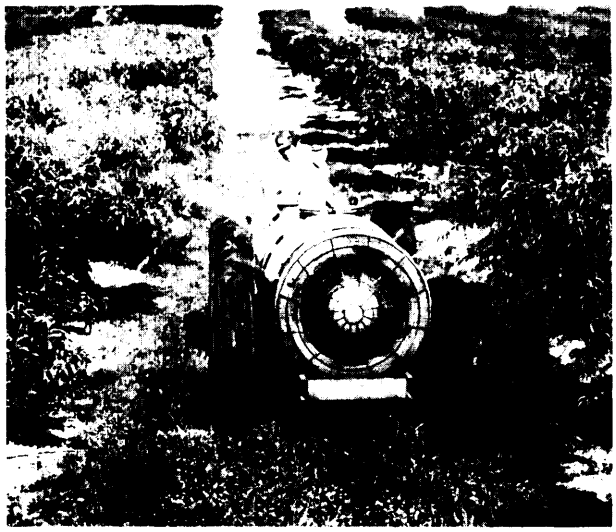


Photo credit: Grant Heilman, Inc.

Chemicals applied during production of fruits and vegetables may affect certain grade criteria. Enhanced grade quality is one of many reasons for using pesticides.

disparity reflects differences in the size of the market and the higher profitability of the herbicide class, which encourages new product innovation. Development of new fungicides is tricky due to a tendency for the development of pest resistance. Finally, fungicides have faced significant regulatory problems due to high carcinogenicity or oncogenicity. Although important to the production of fruits and vegetables, introduction of a new fungicide product can be a financial risk for the developing company.

Production of processing tomatoes in California and fresh market tomatoes in Florida and Ohio are discussed to highlight patterns of fruit and vegetable fungicide use. About 1.3 million tons of active ingredients are applied to the 304,000 acres devoted to these crops. California, which has 240,000 acres in processing tomatoes, uses 784 tons of fungicide active ingredient. On a pound-per-acre basis, however, the State uses only 6.5 lb per acre, compared to 11.5 lb per acre in Ohio and 17.9 lb per acre in Florida. The higher application rates in Ohio and Florida are due in part to the more rigid cosmetic requirements needed for fresh market production. More importantly, the more humid Midwestern and Southern climates necessitate increased levels of fungicide use.

The fungicide use pattern of tomatoes is representative of most fruits and vegetables. California uses less per acre because of its dry, favorable climate. But because it produces over half of the Nation's fruits and vegetables, California utilizes the largest share of fungicide products applied nationwide.

Pesticides and the Current Grading System

Chemicals applied during production may affect certain grade criteria in the current USDA grade standards for fruits and vegetables. An assessment of the relationship among various chemicals and current grade criteria was completed for apples, potatoes, and tomatoes. Tables 14-1 2–14- 14 summarize current, recommended cultural practices and the relationship of the chemical to current, selected USDA grade criteria. An ''X' is placed in each cell where the chemical's use affects the particular grade criterion. The summary reveals that chemical use primarily is relevant to three general grade criteria—fungus injury, insect injury, and decay. Thus, chemicals are used primarily to protect potatoes and tomatoes from fungal or insect damage.

While relationships between pesticide usage and grade criteria have been found, it is not clear whether or not current grade criteria encourage use of pesticides. Probably, improved grade quality is only one reason for using pesticides. Other reasons would likely include higher yield, better harvesting conditions, and reduced pest preserves on subsequent crops.

Chemical Residue Grading Standard

For an attribute to serve as a portion of a grade standard, variation in the attribute is necessary. Two recent surveys of chemical residues in food suggest that individual samples of fruit and vegetables are likely to exhibit differences in chemical residues. In 1989, the State of California sampled 9,403 food samples for pesticide residues (43). The following distribution was found:

Residue distribution	Percent of *samples*
No detectable residues	77.9
Residues 10% or less of tolerance level	13.0
Residues between 1O%. and 50% of tolerance level	7.4
Residues from 50% to 100% of tolerance level	1.0
Exceeded tolerance level	0.7

FDA annually tests about 20,000 samples of fresh and processed foods for residues exceeding tolerances established for 10,000 food additives and 300 pesticides (51). Foreign food imports make up a large proportion (36 percent) of the samples. In 1988, no residues were found in 60 percent of the samples tested. The remaining 40 percent contained detectable residues,

Table 14-12-Relationship Among Selected USDA Grade Criteria and Chemicals Approved for Use on Apples, Ohio, 1991

Chemical (Scientific Name)	Selected generic grade criteria				
	Maturity	Fungus injury	Decay	Insect injury	Size[a]
Growth regulator					
Fruitone N (1-Naphthalene-Acetic Acid)	x				
Herbicides					
Gramoxone (Paraquat) (Bipyridylnium)					x
Sinbar (3-tert-Butyl-5-chloro-6-methyluracil)					x
Karmex (Substituted Urea)					x
Fungicides					
Captan (Cis-N-trichloromethylthio-4-cyclohexene-2 1,2-dicarboximide)		x	x		
Benlate (Methyl-1 (butylcarbamoyl)-2-benzimidazolecarbamate)		x	x		
Dithane (Ethylene bisdithiocarbamate)		x	x		
Insecticides					
Oil (Oil solutions)			x	x	
Guthion (Organophosphorous-Pesticide family)			x	x	
Vendex (Organotin)			x	x	
Imidax (N-(Mercaptomethyl) phthalimide S-O, O-dimethylphosphorodithioate)			x	x	

[a]Very poor weed control can result in smaller size because of competition between weeds and the commercial crop.

SOURCES: Office of Technology Assessment, 1992, compiled from Ohio Crop *Enterprise Budgets, 1989: Specialty Crops,* The Ohio State University, Columbus, OH, p. 30 and *Farm Chemicals Handbook,* Meister Publishing Co., 1991.

but less than 1 percent of the samples exceeded EPA tolerances.[5]

EPA regulations exclude from the human food supply any commodity for which safe chemical residue levels are exceeded. This is not a grading question, but a food safety concern. However, assuming that the safe level for detectable residue is greater than zero, a grading standard hypothetically could be established on the basis of detectable levels of a specific chemical residue. The degree of detectable residue denotes a particular grade category. A hypothetical example appears in table 14-15.

Table 14-15 indicates that, if the level of detectable chemical residue were the only attribute used for grading, higher grades would be assigned to foods with successively lower residue levels.

Conceptually, each type of chemical would constitute a separate attribute. The set of chemicals deemed appropriate would then compose the standard. Another possibility would be to develop a summary index or weighted average measure for chemical residue. Such a summary index could allow the resultant grade to be assigned on the composite or summary score.

Conclusions

Implementation of a chemical residue attribute standard for fruits and vegetables would require decisions concerning which chemicals would form the standard. This task would be controversial and would require participation from a broad array of interested parties. It is reasonable to assume that some potentially usable chemicals would not be admitted to form the standards.

If a chemical residue grading system were implemented, lack of inclusion of naturally occurring toxic substances would be controversial. Naturally present phenolic compounds in fruits and vegetables have been found to be carcinogenic. Flavinoids tuercetin and campherol are present in many fruits and vegetables. Acetaldehyde, found in apples, is reported to be mutagenic. Aflatoxin is a fungal toxin and known carcinogen that can and does occur in virtually every fruit and vegetable from the fresh to processed state. Thus, a grading standard based on residues of chemicals ideally should include naturally occurring as

[5]Of the samples that exceeded tolerance levels, 84 percent involved cases for which there was no established EPA tolerance. Lack of an EPA tolerance level generally means that any residue deems the commodity to be "adulterated" and subject to regulatory action. Exceptions include "Unavoidable Pesticide Residues," which result unavoidably in certain processes under "good" agricultural and manufacturing procedures, and EPA "Emergency Exemptions," which are granted for use of nonregistered pesticides under certain emergency situations.

Table 14-13—Relationship Among Selected USDA Grade Criteria and Chemicals Approved for Use on Potatoes, Ohio, 1991

Chemical (Scientific Name)	**Selected** generic grade criteria				
	Maturity	Fungus injury	Decay	Insect injury	Size[a]
Vine Killer Dessicant					
Diquat (1,1 '-ethylene, 2,2' bipyridyliomion)[b]	x				
Herbicides					
Lorox (Linuron & Chlorimuron Ethyl)					x
Dual (Chloracetanilise)					x
Eptam (S-Ethyldipropylthiocarbamate)					x
Sencor-Lexone (Triazinone)					x
Fungicides					
Bravo (Chlorohalonil)		x	x		
Ridomil (Metzlaxyl & Mancozeb)		x	x		
/insecticides					
Di-Syston (Organophosphorous)			x	x	
Sevin (Carbamate)			x	x	
Phorate (Organophosphate)			x	x	
Guthion (Organophosphorous)			x	x	
Cygon(Carbamate)			x	x	

[a]Very poor weed control can result in smaller size because of competition betweenweedsandthe commercial crop.
[b]Diquat is also applied to set potato skins.

SOURCE: **Office of Technology Assessment, 1992, compiled from Ohio** *Crop Enterprise Budgets, 1989:* **Specialty Crops, The Ohio State University, Columbus, OH, p. 16 and** *Farm Chemicals Handbook,* **Meister Publishing Co., 1991.**

Table 14-14-Relationship Among Selected USDA Grade Criteria and Chemicals Approved for Use on Staked Fresh Market Tomatoes, Ohio, 1991

Chemical (Scientific Name)	**Selected** generic grade criteria			
	Fungus injury	Insect injury	Decay	Size[a]
Herbicide				
Treflan (3,3,3-trifluoro-2,6-dinitro-N, N-propyl-p-toluidine)				x
Fungicides				
Bravo (Chlorothalonil)	x		x	
Benlate (Methyl-1 (butylcarbamoyl) -2-benzimi-dazolecarbamate)	x		x	
Insecticides				
Sevin (Carbamate)		x	x	
Thiodan (Chlorinated Bicyclic Sulfite)		x	x	

[a]Very poor weed control can result in smaller size because of competition between weeds and the commercial crop.

SOURCE: Office of Technology Assessment, 1992. Compiled from *Ohio Crop Enterprise Budgets, 1989:* ***Specialty Crops*****, The Ohio State University, Columbus, OH, pp. 3–5 and** ***Farm Chemicals*** *Handbook,* **Meister Publishing Co., 1991,**

well as synthetic toxic substances. [b] Such a standard would be complex and controversial.

Options for an Improved Grading System

The purpose of the case study to this point has been to introduce the conceptual basis for two different fruit and vegetable grade standards—one based on nutritional content, the other on chemical residues. The investigation has determined three requirements for an attribute to serve, in whole or in part, as a grade standard. One requirement is that the attribute must vary across the produce to be graded. A second requirement is that information on the attribute must exist so that preferences can be assigned to gradations of an attribute. The third requirement is that the attribute must be measurable.

The assessment of conceptual alternatives has established that both nutrition and chemical residue attributes

[6] An argument can be made that humans have evolved over a long period of time eating these foods and have adapted to them and the chemicals in them. But humans have not evolved with pesticides so the impacts can be different.

Table 14-15-Hypothetical Example of Grading System Based on Chemical Residues

Level of detectable chemical residue	Resultant grade
Greater than EPA established residue tolerance level	No grade, excluded from human food supply
<49% safety level	Grade C
50-90% safety level	Grade B
>90% safety level	Grade A

SOURCE: Office of Technology Assessment, 1992.

could be expected to vary across types of produce. Thus, the first requirement is met.

The second and third requirements are more complex and difficult to assess. The scientific literature review contained in this chapter reveals substantial gaps in the knowledge base required for either grading alternative.

Measurement, as a third requirement for an alternative grade standard, is a special issue. Current standards that primarily rely on sensory attributes mean that human graders can gauge the presence or absence of the attribute without mechanical assistance. Neither of the alternative standards is sensory in nature, implying the need for mechanical measurement. This, in turn, has significant implications for the viability and cost effectiveness of either alternative, given today's technology.

Mechanical measurement or testing likely would be slower and more costly than conventional grading by humans. Lower efficiency and consequent higher grading costs would probably occur for either the chemical residue or nutrition-based alternatives. This would raise consumer prices for fruits and vegetables.

The relative merit of implementing either alternative for fresh versus processed fruits and vegetables bears analysis. Consumers who purchase fresh produce at retail for at-home consumption presumably would benefit the most from information embedded in either alternative standard. Processing firms and firms in the food service industry (hotel, restaurant, and institutional away-from-home market) already can and often do test produce they purchase for nutrient or chemical residue characteristics. In addition, since nutritional labels are on most processed food products, a nutrition-based standard for processed grades would be redundant and of little value to the ultimate consumers.

OTA concludes that insufficient justification exists to recommend shifting away from the current sensory standards to either of the alternatives discussed here for the processed and food service markets. The argument for alternative grading for the retail at-home (fresh) market segment has more viability, and the ensuing discussion is limited to that portion of the market.

The chemical residue concept for a grading system combines the issue of food safety with that of food quality. The current food distribution system treats food safety and quality separately. That is, the current distribution and marketing system essentially assigns grades only to food determined safe for human consumption. The ''mixing' of these issues distinguishes the chemical residue attribute from the existing system.

The objective of implementing such a standard would be to provide consumer information on the amount of detectable residue below some "safe" level. Presumably this would allow consumer choice among various levels of ''safe for human consumption residue' at alternative prices. However, the chances for consumer misinformation from such an attribute probably would be quite high. Consumers could easily misconstrue the information to mean that some foods on the market are not safe. Because of these problems, the chemical residue base for standards is dismissed as a viable alternative by OTA, even for the retail at-home fresh fruit and vegetable market segment.

Thus, three viable policy options arise from this analysis: abolishing current retail grades and standards, relying on point-of-sale (POS) nutritional labeling, and modifying the current Federal standards to reflect some information on nutrient content. An evaluation of each policy option follows.

Option l—Abolishing Grades

Consumer grade standards exist, but seldom are used. Explanations that might account for the limited use of consumer grade standards include the following:

- retail grades are not useful as a merchandising device, and
- retail grades do not convey any additional information beyond that embodied in wholesale grades.

Regardless of the reasons for lack of use of retail grades, it is clear that abolishing them would not have a direct and significant impact on the marketing of fruits and vegetables.

Because grade standards are used extensively for wholesale trading, abolishing wholesale grades would have significant economic consequences for the fruit and

vegetable industry. Some immediate and obvious consequences would result:

- transactions costs associated with trades would increase.
- marketing efficiency would decline.
- marketing information would become less meaningful because price differentials by quality would be less accurate, and
- fewer buyers would be available for a given seller (i.e., geographical area of trades would diminish).

Without the impartial information conveyed through grade standards, fruit and vegetable marketing would experience a significant decline in overall efficiency. Commodities previously bought by grade descriptions would require inspection by buyers, producing a decline in the efficiency with which fruits and vegetables are shipped from production areas to consuming areas. Such inspection also would reduce the area over which commodities could be traded, thereby limiting market competition and raising commodity prices at the wholesale and retail level. Moreover, while the current grading system facilitates grading at the shipping point level, abolishing grades would encourage trade consummation at terminal markets. Previous experience has already shown that terminal market transactions are less efficient than the current geographically dispersed system (i. e., most produce bypasses terminal markets because chain stores buy direct from shipping point markets).

Although grade standards primarily are used to facilitate wholesale trading, abolishing them is likely to have significant impact at the consumer level. For example, one reason grades might not be used at the consumer level is that their use at the wholesale level captures the relevant attributes for consumers. That is, attributes such as color, maturity, shape, and size, which facilitate wholesale transactions, are likely to be important for consumer transactions. If these attributes are not used for wholesale transactions, then consumer purchases at the retail level that are based on these attributes are likely to be impeded.

Option 2—Point of Sale Nutritional Labeling

The U.S. Congress in 1990 passed and the President signed a fruits and vegetables nutritional labeling law. The law stipulates that the content, format, and delivery of fruit and vegetable nutritional labeling is to be determined by the Food and Drug Administration (FDA). In general terms, the bill will require the posting of point of sale (POS) signs that detail the nutritional content of the 20 most frequently consumed fruits and vegetables. During an 18-month period following signing of the law, compliance is voluntary. Should compliance be deemed insufficient, a provision in the **law** enables the FDA to then make in-store nutritional labeling mandatory.

The bill had the general support of industry trade associations such as the United Fresh Fruit and Vegetable Association, the Produce Marketing Association, and the Food Marketing Institute. The final compromise legislation proved to be less onerous than earlier versions of the bill, which would have called for labeling of virtually all produce sold in stores. The trade associations view labeling as positive because of the opportunity to present information highlighting the nutritional benefits of produce. The conclusion drawn by the produce industry, in terms of labeling's potential impact on sales, is that to the extent that consumers are better informed about the nutritional quality and healthful benefits of fruits and vegetables, overall sales of fruits and vegetables should go up. These indusry groups, however, do not support the idea of mandatory labeling and therefore are working to assure high voluntary compliance. Additionally, they seem to be advocating simplified labeling with information on calories, carbohydrates, fiber, vitamin A, and vitamin C.

The production of nutritional labels (signs) that presumably would be posted in every retail food store in the country under this legislation will entail significant startup costs. Once the labeling system has been put into place, maintenance costs should be modest. The nutritional components of the produce to be displayed in the labeling will come from government published data, and the signs (or labels) themselves will become permanent fixtures within produce departments. Open to question is the extent to which implementation costs may be passed on to consumers. Little direct cost will be incurred by produce retailers. The labeling will be provided by various industry trade associations, and the signs and labels should be freely available in the 18-month "voluntary" initial phase of the law as the various industry groups are interested in bolstering participation to stave off mandatory labeling.

The final form nutritional labeling will take is still being worked out between the FDA and interested industry and consumer advocacy participants. The produce industry perceived several years ago that nutritional labeling was an inevitability. By becoming involved with nutritional labeling in its early stages, the industry can exert influence on the form nutritional labeling would take.

A survey by Opinion Research Corp. commissioned by the National Food Processors Association in late 1989 found that 4 of 10 consumers say that the first time they buy a food product they read the labels for general nutritional information and make purchasing decisions based on their comparisons. The survey results report that the more nutritionally sound a food product is (e. g., breakfast food v. snack food), the more likely consumers are to buy it. Other research has revealed that perceived negative food attributes such as high sodium or cholesterol contents are just as important as positive attributes in formulating consumer decisions to buy one food product over another. Significantly, the proposed produce labeling is limited to nutritional attributes perceived by consumers to be positive.

The final form that nutritional labeling will take may favor some fruits and vegetables over others in marketplace competition. First, determining which are the top 20 fruits and the top 20 vegetables by consumption is difficult: there seems to be some jockeying for a place among positions 15 through 20. In these lower ranking categories, consumption statistics do not indicate clear winners. Foods that do carry nutritional labels probably will attract consumers and lead to sales increases at the expense of the lower rated foods. A second important implication of nutritional labeling in terms of marketplace competition relates to display of the nutritional information. Will labeling take the form of presentation of aggregate data at a centralized location, with the 40 produce products ranked on attributes; or will each produce bin have a unique sign with nutritional attributes displayed solely for that product? Research indicates that, for aggregate data, sequencing would have an impact on consumer purchase decisions. If, for example, ranking occurred on a positive (negative) nutritional attribute, then consumers would be steered toward (away from) purchase of the higher ranked food.

The nutritional labeling law will present the FDA with another program area to administer. Therefore, some governmental costs will be incurred. After FDA's initial involvement of writing provisions of the legislation, however, its involvement will be limited to measuring compliance. Should the labeling legislation become mandatory, then it is possible that administrative costs related to enforcement could rise.

Option 3—Modifying Grades

Basing Federal fruit and vegetable grades for the at-home retail market in part on nutrient characteristics presents an interesting and plausible option. The scientific knowledge base for this option is relatively adequate though not comprehensive in scope. The possibility of combining some nutrient attributes with existing sensory characteristics appears feasible. For example, the relationship between maturity in the current standards and several nutrient attributes is fairly well established.

The economic impact and cost of adjustment to some nutrition-based grade standards, especially if they were mandatory, would be substantial. Transactions costs would increase for some period of time during adjustment to the new standards. Costs of grading would increase, especially if destructive testing for nutritive content were necessary. Consequently, during the adjustment period, prices for fresh fruits and vegetables at retail likely would be higher and producer prices lower.

After some period of adjustment, nutrition-based grading standards would become customary for all firms involved in the marketing channel-producers, wholesalers, and retailers. At this point, transaction costs of using the new system should not be significantly different from the previous sensory standards; however, grading costs would be higher because nutrition-analysis requires the use of instruments and experts. These increased transactions costs would be passed on to consumers in the long run.

The distribution of costs to various industry participants would be different during the adjustment period than in the long term. Initial uncertainty about the new standards would increase transaction costs to users of the new standards. If use of the new standards were voluntary, relatively higher transaction costs would discourage use of the new system by wholesalers and retailers. Instead, they would use the former standards or rely on trade associations or comparable groups to define standards similar to the old system. Furthermore, over the longer term, the higher transaction costs would result in higher costs to consumers and/or lower prices for producers.

The shift to a grading system based in part on nutrition criteria would probably diminish the historic role the Agricultural Marketing Service has played in grading and enhance the role of FDA. The food science component of FDA would be a more natural focal point for regulatory and compliance activities.

Conclusions

A summary table of the conclusions concerning the potential viability of the alternative conceptual bases ex-

Table 14-16—Summary Conclusions on Potential Viability of Conceptual Grading Alternatives

Market segment	Chemical base	Nutrient base
Fresh	Costly to implement	Costly to implement
At-Home	Sparse scientific knowledge base May impart misleading information	Inadequate current scientific knowledge base Advantage lessened by recent nutritional **information point-of-sale program** **Relatively most viable**
Away-from-Home	Marginal value to consumers Costly to implement	Marginal value to consumers Costly to implement
Processed	Marginal value to consumers Costly to implement	Marginal value to consumers Costly to implement

SOURCE: Office of Technology Assessment, 1992

amined is presented in table 14-16. Before either the nutrient or chemical base could be implemented on a cost-effective basis, advances in measurement technology would need to occur. This is on the horizon, but until advances occur, the wisdom of adopting an alternative base seems marginal from a societal perspective. At the current time, neither the scientific information base or the technology for measurement permits nutrient attributes to be an exclusive grade standard for fruits and vegetables.

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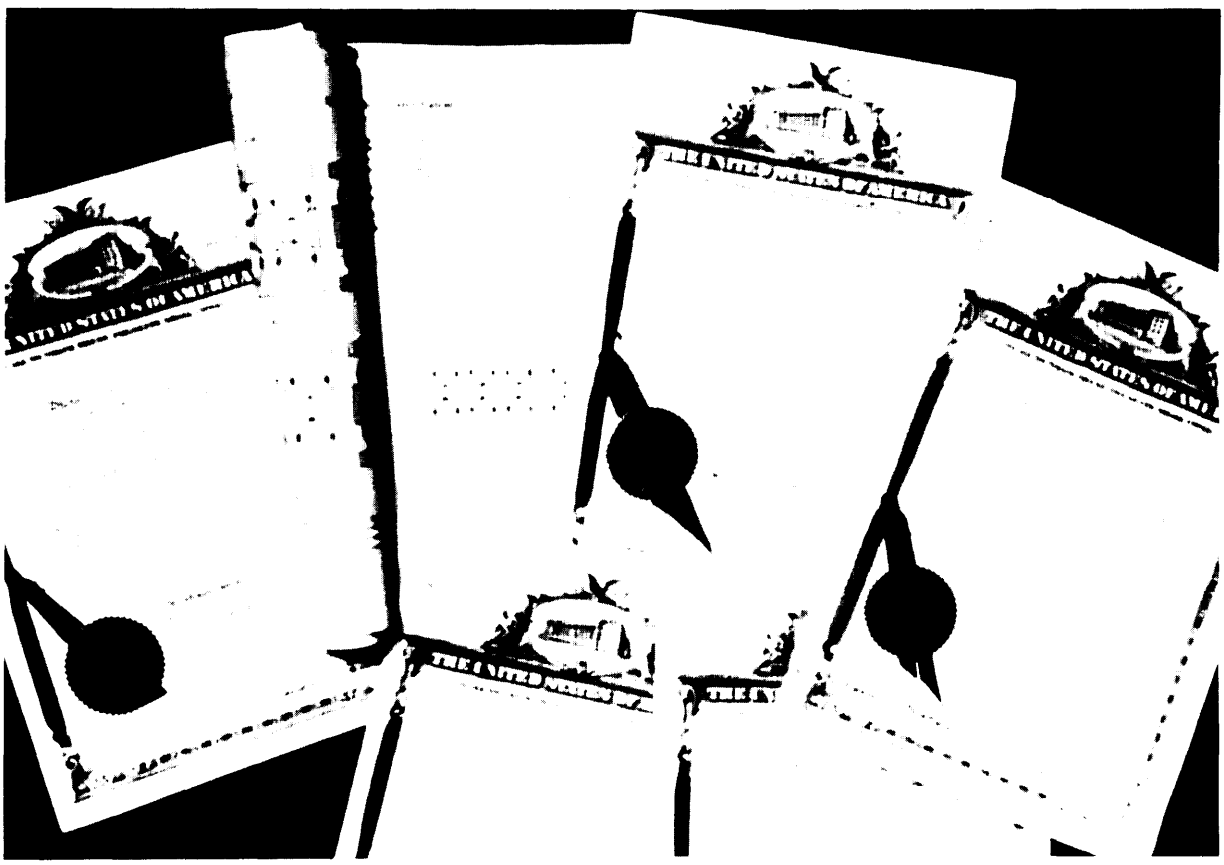
Part V

Institutions

Chapter 15

Intellectual Property Rights for Biotechnology and Computer Software



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INTRODUCTION

Biotechnology and advanced computer technologies have the potential to carry the productivity record of agriculture into the 21st century. Biotechnology can increase food production by lowering the costs of agricultural inputs and by contributing to the development of new high-value-added products to meet the needs of consumers and food processors. These potential products include seeds, pesticides, veterinary diagnostics and therapeutics, food additives and food processing enzymes, more nutritious foods, and crops with improved food processing qualities. Advanced computer technologies can enhance management capabilities in the agriculture and food industry. These technologies include knowledge-based systems, networks, information retrieval systems, sensors, and robotics.

Thus far, biotechnology research and development (R&D) has focused on those crops and traits that are easiest to manipulate, particularly single-gene traits in certain vegetable crops. As technical roadblocks are lifted, however, R&D likely will lead to a wide range of agricultural products. Likewise, computer software R&D and further advances in networks, sensors, and robotics will spawn numerous computer-related technologies for food and agricultural use. A critical incentive for R&D efforts in biotechnology and information technology is adequate intellectual property protection for these emerging processes and products.

Intellectual property law, which protects works of the mind as personal property, is of increasing importance to those who create new products and processes using biotechnology and computers. Intellectual property involves several areas of the law: patent, copyright, trademark, trade secret, and plant variety protection. All affect emerging high-technology industries and can help bring important technological information and products into commerce. This chapter examines intellectual property rights for inventions created through the use of biotechnology (with particular focus on plants and animals) and computer-related technologies.

INTELLECTUAL PROPERTY PROTECTION AND BIOTECHNOLOGY

Intellectual property protection encompasses several areas of statutory and common law: patent, copyright, trademark, trade secret, and plant variety protection; other laws discourage unfair competition. Patents, trade secrets, and plant variety protection are particularly important to biotechnology.

Patents

United States patent law has its roots in the Constitution, which gives Congress broad powers to ''promote the Progress of Science and useful Arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries' (article 1, section 8). The first patent act was enacted by Congress in 1790 and, though amended several times, still allows broad scope as to what can be patented. (See box 15-A).

A patent is a grant issued by the U.S. Government that gives the patent owner the right to exclude all others from making, using, or selling the invention within the United States, its territories, and possessions during the term of the patent (35 U.S. C. 154). There are three types of patents. The most common type is the utility patent. To qualify for utility patent protection in the United States, an invention must meet several requirements:

Box 15-A—What Can Be Patented?

One section of the U.S. patent law, 35 U.S.C. 101, defines what constitutes a patentable invention:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

This section of the patent code has changed little since it was first enacted in 1790, and its broad language has made possible the issuance of more than 5 million patents.

SOURCE: Office of Technology Assessment, 1992.

The U.S. Constitution provides that "Congress shall have the power. . . . To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries."

- it must be a process, machine, manufacture, or composition of matter (35 U.S.C. 101);
- it must be new, useful, and not obvious (35 U.S.C. 101-103); and
- it must be disclosed in sufficient detail to enable a person skilled in the same or the most clearly related area of technology to construct and operate it (35 U.S.C. 112).

A second category, patents for plants, includes cultivated sports, mutants, hybrids, and newly found seedlings. A third category, patents for designs, is not relevant to biotechnology-related inventions.

Patents serve two important policy objectives:

- by rewarding successful efforts, a patent provides inventors and their backers with incentive to risk time and money in R&D; and
- by requiring disclosure of the manner and process of making an invention, a patent encourages public disclosure of otherwise secret information, so that others are able to use it.

Although a patent gives the inventor the right to exclude others from making, using, or selling the invention for 17 years, it does not grant the inventor any affirmative right to make or use an invention. Commercial use of a patented invention, just like other products, can be regulated by Federal, State, or local law.

Once obtained, a patent has a term of 17 years, assuming that maintenance fees are paid (35 U.S. C. 154). One exception to the 17-year term is relevant to biotechnology: patents on a human drug product, medical device, food, or color additive that have undergone regulatory review prior to FDA approval for commercial marketing or use may be eligible for an extension of up to 5 years, if certain conditions are satisfied (35 U.S.C. 156).

Recent revisions in Federal patent policy have encouraged increased patent activity from federally funded researchers. Prior to 1980, 26 separate patent policies promulgated by various government agencies existed for such research (9). Recognizing that a uniform patent policy would encourage cooperative relationships and commercialization of government-funded inventions, Congress passed the Patent and Trademark Amendments of 1980 (P. L. 96-5 17) and amendments in 1984 (P. L. 98-260). The law allows nonprofit institutions (including universities) and small businesses to retain title to patents arising out of federally funded research, with the Federal agency retaining a nonexclusive, worldwide license. Universities are required to share royalties with the inventor and to use any net income for research and education (35 U.S.C. 202).

The law, which gave statutory preference to small businesses and nonprofit organizations, was extended by executive order to larger businesses in 1983 (6). The Technology Transfer Act of 1986 (P. L. 99-502) granted Federal authority to form consortia with private concerns. Executive order 12591, issued in 1987, further encouraged technology transfer programs, including the transfer of patent rights to government grantees.

Trade Secrets

Trade secrets extend protection to information used in one's trade or business, that is maintained in secret by its owner, and provides a competitive business advantage over those not having the information. A plan, process, tool, mechanism, recipe, chemical compound, customer list, or formula all are examples of information that can be maintained as trade secrets.

Unlike patents (which are governed exclusively by Federal law), trade secrets are the subject of State law. Trade secret law promotes not only commercial morality and fair dealing, but also research and innovation. Unlike patent law, however, trade secret law discourages rather than encourages public disclosure of technical information.

Trade secret rights require that a trade secret be disclosed in confidence only to those having a reasonable need to know (e. g., employees). Measures must be taken

by the owner of the trade secret to prevent disclosure of the trade secret to the public or to competitors (e.g., expressly identifying the information as a trade secret and prohibiting its disclosure).

The Chakrabarty Decision

During the 1980s, two events in the United States shaped the application of intellectual property law to biotechnology. First, the Supreme Court was called on to determine whether a living organism could be patented. Second, Congress and the executive branch took actions making it easier for federally funded inventions to become commercialized. These actions ignited a flood of biotechnology patent activity. By 1989, an examining unit specifically for biotechnology was established at the Patent and Trademark Office (PO).

The development of rDNA technology in the 1970s led to debate regarding what constitutes a patentable invention. Although patents on biotechnological processes had been issued since the 1800's, PTO did not permit patents on living products created by the technology on the grounds that such matter were ''products of nature' and not statutory subject matter as defined by 35 U.S. C. 101 (see box 15-A). Although proposed patent claims to living organisms were rejected by PTO, patent protection had been granted for many compositions containing living things (e. g., sterility test devices containing living microbial spores, food yeast compositions, vaccines containing attenuated bacteria, milky spore insecticides, and various dairy products) (8).

The issue of whether a genetically engineered organism itself could be patented was addressed by the Supreme Court in 1980, in *Diamond v. Chakrabarty 2).* **In** this case, the patent applicant had developed a genetically engineered, but not recombinant, bacterium capable of breaking down multiple components of crude oil. Because no naturally occurring bacterium possessed this property, Chakrabarty's bacterium was thought to have significant value for the cleanup of oil spills.

Chakrabarty filed a patent application with 36 claims. Process claims for the method of producing the bacteria were allowed by the PTO; but claims for the bacterium, itself, were rejected on two grounds: 1) microorganisms are "products of nature, " and 2) as living things, microorganisms are not patentable subject matter under 35 U.S.C. 101. The case was eventually heard by the Supreme Court; the justices, in a 5-4 ruling, held that a live, human-made microorganism is patentable subject matter under section 101 as a ''manufacture' or ' 'composition of matter. "

The *Chakrabarty* decision provided a judicial framework for subsequent PTO decisions to issue patents under 35 U.S.C. 101 for plants and nonhuman animals. The decision also provided great stimulus for the economic development of biotechnology processes and products in the 1980s.

INTELLECTUAL PROPERTY PROTECTION FOR PLANTS

Plant Breeders' Rights

No intellectual property rights relevant to new plant varieties existed prior to 1930. Plant breeding and research were conducted primarily by federally funded agricultural experiment stations and, to a limited extent, by amateur breeders. Private breeders had few financial incentives—their sole financial reimbursement was through high sales prices of comparatively few reproductions during the first 2 or 3 years after the variety's initial availability. Once the plant left a breeders' hands, it could be reproduced in unlimited quantity by anyone.

Proprietary protection specifically for plant varieties has evolved in the United States over the last 60 years and now is based on several statutes, a Federal decision, and recognized trade secret and contract law. (See table 15-1.) Although in the United States an exclusive right to an invention is as old as the Constitution, until the late 1920s the sentiment was largely held that plant varieties were not patentable under the general patent statute. In deciding to expressly provide intellectual property protection for asexually reproduced plants, Congress concluded that the work of the breeder was an aid to nature and thus the resulting plant was a patentable invention.

Two Federal statutes specifically confer ownership rights to new plant varieties: the Plant Patent Act (PPA) of 1930 (35 U.S.C. 161-164) and the Plant Variety Protection Act (PVPA) of 1970 (7 U.S.C. 2321 *et seq.).* The PPA extended patent protection to most new and distinct asexually propagated varieties. It was the first, and to date, only law passed by Congress specifically providing patent protection for living matter. Since then, more than 6,500 plant patents have been issued by PTO covering flowering plants, ornamental and fruit trees. nut trees, grapes, and vegetable crops. Plant patents cannot be obtained for seeds, tubers, biotechnology processes, recombinant DNA (rDNA), or genes (5). On average, more than 225 plant patents are issued each year (10).

Table 15-1—Types of Intellectual Property Protection for Plants

Type	Citation	Subject matter
Plant patent	**35 U.S.C.** 161-164	Asexually reproduced varieties
Plant variety protection certificate	7 U.S.C. 2321 *et seq.*	**Sexually reproduced varieties**
Utility patent	**735 U.S.C. 101 et** *seq.*	**Process, machine, manufacture, composition of matter**
Trade secret	**State law**	**Information used in trade or business that is kept secret**

SOURCE: Office of Technology Assessment, 1992

Commercial and international developments between 1930 and 1970 encouraged the United States to consider protecting sexually reproduced plants as well. Plant breeders had developed new sexually reproducing plants that could replicate ''true-to-type' but that could not be patented under the PPA. In 1961, several European countries formed the International Union for the Protection of New Varieties of Plants (UPOV) to protect breeders' rights. (See box 15-B.) At the time, U.S. breeders had no law protecting their inventions, other than the PPO for asexually reproduced plants.

The PVPA was enacted by Congress in 1970 to provide patent-like protection for certain types of new, sexually reproduced plant species. It is mainly of interest to breeders and farmers of sexually reproduced varieties of crops such as: wheat, alfalfa, soybeans, cotton, corn, lettuce, soybeans, and watermelon (1).

Although PVPA is not a patent statute, the protection it provides to breeders of new plant varieties is similar in concept to patent protection. The act is administered by the U.S. Department of Agriculture (USDA). Upon application to USDA and examination by this agency, a plant variety protection certificate may be issued on any novel variety of sexually reproduced plant—other than fungi, bacteria, or a first-generation hybrid. The novel variety must have distinctiveness, uniformity, and stability. Amendments in 1980 (P. L. 96-574) added protection for six vegetable crops and extended coverage to 18 years so the PVPA would be consistent with UPOV provisions.

Under PVPA, the breeder can exclude others from selling, offering for sale, or reproducing (sexually or asexually) the variety; producing a hybrid from the variety; and importing or exporting the protected variety.

PVPA contains two important exclusions to this protection:

- **A research exemption** that precludes a breeder from excluding others from using the protected variety to develop new varieties; and
- **a farmers' exemption that allows** an **individual whose primary occupation is** growing crops for sale, for other than reproductive purposes, to use protected seed on his or her farm or to sell it to people whose primary occupation, also, is growing crops.

From 1970 through 1988, 2,783 applications for plant variety protection certificates were filed with the USDA for some 100 different crops. By December 31, 1988, 2,133 certificates had been issued and 274 applications were pending. Another 376 applications had been abandoned, withdrawn, declared ineligible, or denied (10).

The Supreme Court decision in *Diamond v. Chakrabarty (2),* coupled with a 1985 ruling of the *PTO* Board of Appeals (3), affords individuals the additional option of seeking a utility patent (35 U.S.C. 101) to protect a novel plant variety. In 1985, the PTO Board of Appeals and Interferences ruled, in Ex *parte Hibberd (3)* that a corn plant containing an increased level of tryptophan, an amino acid, was patentable subject matter under 35 U.S.C. 101. To summarize, federally credentialed protection of plants encompasses three forms: plant patents, plant variety protection certificates, and utility patents. Recognized trade secret law provides further protection for inventions that constitute plant life. Each of these four methods of protection differs from the others in some respects, as described below.

Plant Patents v. Plant Variety Protection Certificates

PPA provides rights, through plant patents, to plant breeders who discover or develop new distinct plant varieties and propagate them by asexual reproduction. In contrast, Plant Variety Protection Certificate (PVPC) holders under PVPA are granted protection for discovering or developing new, uniform, stable, and distinctive

Box 15-B—International Union for the Protection of New Varieties of Plants

With the development of plant sciences came the realization that the rights of plant breeders were entirely overlooked in many countries. The patent laws of many countries, for example, specifically excluded the patenting of any type of lifeform. An international conference in 1957 led to the drafting of the International Union for the Protection of New Varieties of Plants (UPOV); it was signed by several nations in 1961 and entered into force in 1968. Currently, 19 nations are members of UPOV (see table 15-2).

Table 16-2-Member Countries of the Union for the Protection of New Varieties of Plants

Australia	The Netherlands
Belgium	New Zealand
Denmark	Poland
France	South Africa
Germany	Spain
Hungary	Sweden
Ireland	Switzerland
Israel	United Kingdom
Italy	United States
Japan	

SOURCE: Office of Technology Assessment 1992.

The International Union for the Protection of New Varieties of Plants was designed "to recognize and to ensure the breeder of a new plant variety. . . the right to a special title of protection or of a patent." The goal was to provide a model for the adoption of breeders' rights statutes in individual countries and to assure reciprocity between countries in the convention.

To obtain protection in each member country, it is currently necessary to file a separate application in each country. There is no central filing system, nor is international protection available by filing in only one member county. While both sexually and asexually reproduced plants can be protected, the UPOV convention requires that each protected variety have a specific, unique name for registration purposes. In all member nations except the United States, new varieties are subject to official inspection establishing that conditions for protection are satisfied.

The UPOV convention presently is under consideration for revision. A recent diplomatic conference, held in March 1991, may lead to revision of Article 2, which currently does not allow both patent and breeders' rights for the same botanical species or genus (14).

SOURCE: Office of Technology Assessment, 1992.

plant varieties that are propagated by sexual reproduction. Protection under PPA and PVPA complement each other in providing protection for all new varieties of plants—asexually reproduced by plant patents and sexually reproduced by PVPCs.

Plant Patents v. Utility Patents

Utility patents provide protection for plants, including asexually reproduced plants such as those included within PPA, as well as plant parts (e.g., flowers, fruits, and nuts) and hybrids, which are excluded from PPA. Also, seeds and plants with defined physical traits can be protected through utility patents. Utility patents for plants, when the requirements can be satisfied, offer broader coverage than would be available for the same plant under PPA.

Advantages of obtaining a utility patent for an asex ually reproduced plant are many. A plant patent is limited to a single claim; a utility patent need not be so limited. Perhaps the most significant advantage of the utility patent is that it provides broad protection for inventions that can affect more than a single variety and can cover plant parts including flowers, nuts, fruits, and cuttings that do not asexually reproduce a plant. Further, no requirement exists for utility patents that an infringing plant be reproduced asexually from the patented plant, hence sexual reproduction of the protected variety is also covered.

One disadvantage of utility patents is that the description requirement is more stringent than it is for a plant patent. To satisfy this requirement for utility patents,

placing the plant or seed on deposit may be necessary (depending on whether or not the production of the plant can redescribed by words alone).

Plant Variety Protection Certificates v. Utility Patents

Compared to PVPCs, several aspects of utility patent coverage for sexually reproduced plants appear advantageous to plant breeders. A utility patent is not limited to the specific variety described; it can protect the specific variety, as well as other varieties having the same traits and functional properties. Hybrids are specifically excluded from plant variety protection but are fully protectable by utility patents. Extensive scope of coverage is another significant advantage of utility patents over PVPCs. Utility patents can protect the plant, seed, plant parts, genes, plants having a specific physical trait, and processes for developing new varieties and hybrids.

Another key difference is that utility patent statutes do not provide for a farmer's exemption. Consequently, if anyone other than the patent owner makes, uses, or sells the seed for reproductive purposes, it is an infringement of the utility patent, subject to judicial enforcement. Utility patents also do not allow research exemptions (i. e., it is an infringement of the utility patent to use the patented plant or variety in developing a new variety or hybrid). Finally, compulsory licensing cannot be mandated by any Federal agency for a utility patent. In compulsory licensing under PVPA, the Secretary of Agriculture directs the PVPC holder to grant a license to a third party if the Secretary determines that such a license is in the public interest. The owner receives a reasonable royalty but has no option and must grant the license.

An advantage of PVPCs over utility patents is that the latter have stringent description requirements that may necessitate the deposit of the plant or seed, such that it is publicly available when the utility patent issues. The present Plant Variety Protection Office (PVPO) policy is not to make most deposited seed available to the general public. One other advantage of PVPCs is that protection is afforded to the new variety before the issuance of the certificate (10).

Trade Secret Law

While patents and protection certificates have been applied successfully to plants, they are ill-suited to trade secret protection. Plants often cannot be easily confined to an enclosed space, thus making them susceptible to theft by outsiders. Some plants are easily grown from only a portion of the parent or, if the plant is an inbred, from a seed—if someone obtains inbred seeds, plants from those seeds can be easily reproduced. Theft of secret plant varieties jeopardizes producers' potential compensation for their investment of creative effort, time, and dollars. Nevertheless, some inventors within the agricultural and horticultural industries successfully employ trade secret protection by not releasing the parents of hybrids that they sell.

INTELLECTUAL PROPERTY PROTECTION FOR ANIMALS

in April 1987, the Board of Patent Appeals and interferences ruled that it would henceforth consider nonnaturally occurring, nonhuman, multicellular living organisms, including animals, to be patentable subject matter under general patent law. This statement initiated broad debate and the introduction of legislation concerning the patenting of animals. The first—and, to date, only—animal patent was issued in April 1988 to Harvard University for mammals genetically engineered to contain a cancer-causing gene (see box 15-C). Exclusive license to practice the patent went to duPont Co., which was the major sponsor of the research. The patented mouse was genetically engineered to be unusually susceptible to cancer, thus facilitating the testing of carcinogens and of cancer therapies. Specifically, the patent covers

> . . . a transgenic nonhuman eukaryotic animal (preferably a rodent **such as a mouse) whose germ cells and somatic cells** contain an activated **oncogene sequence introduced into the animal . . which increases the probability of the development of neoplasms (particular] y malignant tumors) in the animal.**

The 1987 PTO policy and the 1988 issuance of the first patent on a transgenic animal spurred public debate on scientific, regulatory, economic, and ethical issues.

Federal Regulation

Several Federal agencies currently use transgenic animals. The National Institutes of Health is currently the largest user of such animals for biomedical research projects. USDA has conducted research on the genetics of animals for many years. USDA's Agricultural Research Service reported projects involving the use of growth hormone in sheep and swine, and chickens engineered by recombinant DNA technology to be resistant to avian leukosis virus. USDA's Cooperative Research Service is in the early stages of supporting extramural research proj-

Box 15-C—Patent Number 4,736,866-The 'Harvard Mouse"

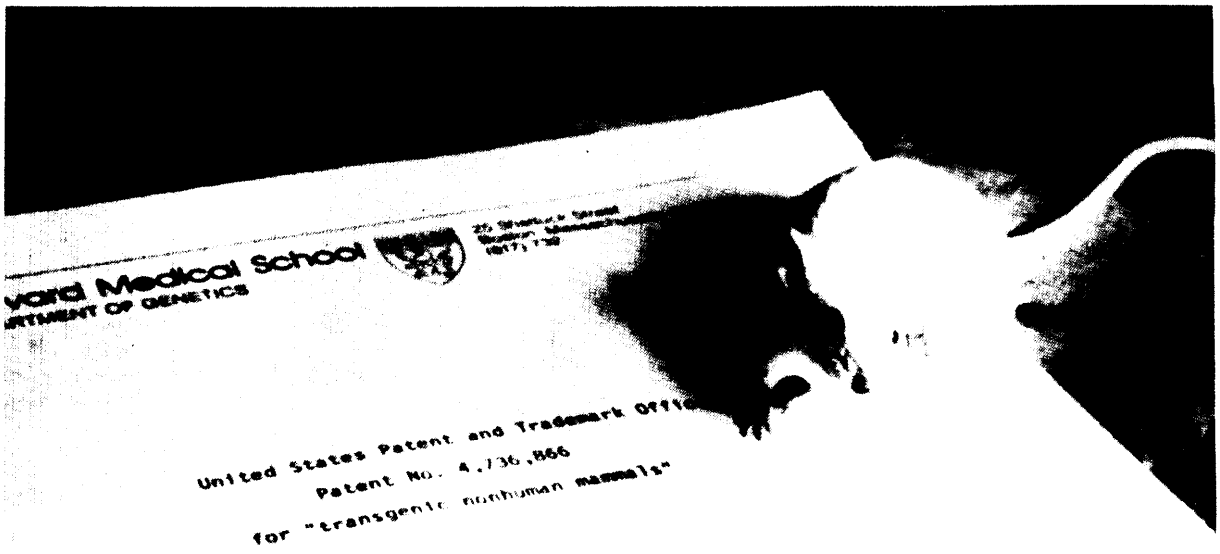

Photo credit: Ira Wyman/Sigma

On April 12, 1988, the U.S. Patent Office issued the first patent of a living animal to Harvard Professor Philip Leder and Timothy A. Stewart of San Francisco, California. The patent was assigned to the President and Fellows of Harvard College. The patent claims "a transgenic nonhuman eukaryotic animal (preferably a rodent, such as a mouse) whose germ cells and somatic cells contain an activated oncogene sequence." The claim cited a mouse into which had been inserted a gene that causes an increased propensity for the mouse to develop cancerous tumors. Such mice can be used to test materials suspected of being carcinogens. These tests "can be extremely sensitive" and "will permit suspect materials to be tested in much smaller amounts . . . used in current animal carcinogenicity studies." The patent points out that this "will minimize one source of criticism of current (testing) methods, that their validity is questionable because the amounts of the tested material used is greatly in excess of amounts to which humans **are** likely to be exposed."

Such transgenic mice "can also be used as tester **animals for materials. . . thought to confer protection against the development of "cancerous tumors (e.g., antioxidants such as beta-carotene or Vitamin E).**

The precise language of the patent described several similar lines of laboratory mice that had been engineered by the insertion of **an** activated oncogene sequence, specifically, the mouse "myc" **myelocytomatosis) gene under control of a promoter or regulatory gene sequence derived from the** mouse mammary tumor virus (MMTV LTR). Gene fusions of the myc and MNITV LTR genes were created and inserted into fertilized one-cell mouse eges via microinjection. The treated eggs were then implanted in receptive female mice and the offspring were raised, used to establish laboratory populations, and then analyzed for incorporation and expression of the inserted genes.

The actual patent coverage is broad, embracing virtually any species of "transgenic nonhuman mammal all of whose germ cells **and somatic cells contain a recombinant activated oncogene sequence introduced into** said ammmal, or an ancestor of said mammal, at an embryonic stage."

SOURCE: U.S. Patent and Trademark Office, U.S. Patent No. 4,736,666 (1966).

ects involving genetically engineered animals. The National Science Foundation (NSF) currently funds research involving transgenic animals in a range of laboratory experiments. With the use of transgenic animals becoming central to whole lines of investigation, NSF expects that work with such animals will increase. The Agency for International Development (AID) funds research involving conventional and transgenic animals at international research centers that are only partially funded by the United States. Accordingly, AID has only partial control over such research activities. Several Federal agencies regulate the experimental use or commercial development of genetically altered animals. Because current statutes regulate various uses and protections for animals, no single Federal policy governs all uses of genetically altered animals. In the absence of a single policy, Federal agencies will rely on existing statutes, regulations, and guidelines to regulate transgenic animal research and product development. Current federally funded research efforts could lead to patents on animals. The patentability of an animal, however, does not affect the manner in which the animal would be regulated by any Federal agency.

Photo credit: Kevin O'Connor

The economics of patenting, such as for these transgenic pigs, will be determined by the potential use of the animal, its market, reproduction rate, and relative value.

Economic Considerations

Economic considerations will influence the order in which different transgenic animals are produced for commerce. Transgenic animals used for biomedical research are likely to be developed first, primarily due to extensive research in this area. Transgenic agricultural animals are also likely to be produced, although large-scale commercial production of such livestock and poultry is unlikely in the near future (5 to 10 years). The largest economic sectors likely to be influenced by animal patents are the different markets for agricultural livestock, and possibly some sectors of the pharmaceutical industry.

The principal agricultural markets involve poultry, dairy, and red meat. These markets are organized quite differently, and they are subject to different degrees of economic concentration. Poultry is the most concentrated (though still diffuse by the standards of other industries, such as automobiles) and the dairy and red meat sectors are more diffuse. Different economic forces are important in these three markets as well: Federal price supports are of major importance in the dairy market, while the market for poultry is more open and competitive. It is difficult to predict the manifold consequences of any particular approach to protecting intellectual property, especially across so wide a range of economic activity as may make use of patentable animals. In addition to the diverse sectors of the agricultural livestock markets, and pharmaceutical and other chemical production, there are academic research or industrial testing activities to consider.

The economics of patenting and the effect on inventors and consumers will be determined by the potential use of the animal, its market, its reproduction rate, and its relative value. The existence of animal patents and the degree to which they are employed in the different markets may introduce some new economic relationships. It is not now clear that these are likely to have any substantially adverse effects on the major markets or existing market forces. The same types of pressures that have driven economic choices in the past are likely to continue to dictate them in the future. If an innovation increases costs (e. g., if a patented animal costs more than the unpatented alternative) it is unlikely to be adopted unless it commensurately increases output or product values. It therefore seems that although cost savings can be anticipated to follow from animal patenting in some areas (e.g., pharmaceutical production or drug testing), innovations attributable to patented animals are likely to advance more slowly in low-margin operations such as raising beef cattle. In some cases, efficient alternatives to protection of intellectual property via patents are feasible. Trade secrets or contractual arrangements might serve well where the animals involved have a high intrinsic value and are limited in number, e.g., animals used for pharmaceutical production. When faced with the complexity of the markets for pork or beef production, however, such alternatives are clearly less practical. However, the same complexity must be accommodated

by any scheme for enforcement or royalty collection associated with patenting animals per se.

Ethical Considerations

A number of ethical issues have been raised in regards to patenting animals. Many of these arguments focus on the human health or environmental consequences that could occur subsequent to the patenting of animals. Other arguments focus on religious, philosophical, spiritual, or metaphysical grounds. These grounds have been used by different parties to support and oppose the concept of animal patenting. Many arguments relating to the consequences of animal patenting are difficult to evaluate since they are speculative, relying on hypothetical scenarios or on as yet unproven assertions. Arguments based largely on theological, philosophical, spiritual, or metaphysical considerations are likewise difficult to resolve, since these may not be acceptable or relevant to other persons holding opposing beliefs. Most arguments that have been raised for and against the patenting of animals concern issues that would be materially unchanged whether patents are permitted or not. Most arguments center on issues that existed prior to the current patenting debate (e.g., animal rights, the effect of high technology on American agriculture, the distribution of wealth, international competitiveness, the release of novel organisms into the environment). It is unclear that patenting per se substantially would redirect the way society uses or relates to animals. Many concerns about the consequences of patenting can be addressed by appropriate regulations or statutes, rather than by amendments to patent law. Other arguments, particularly those of theological, philosophical, spiritual, or metaphysical origin, need to be debated more fully and articulated more clearly.

Deposit Considerations

In 1949, the PTO began recommending that patent applications for inventions involving microorganisms should include the deposit of the pertinent microorganism in a culture depository. A culture depository accepts, maintains, and distributes cultures of microorganisms, viruses, cells, or other genetic-type material. The deposit of seeds and plant tissue culture has become established practice. A depository maybe public or private, nonprofit or for profit. The main function of a public culture depository is the preservation and distribution of reference cultures that serve as standards for users in the scientific and educational communities.

Although not a formal requirement, patent examiners advised applicants that in cases where words alone were not sufficient to describe the invention adequately, a deposit was advisable. Currently, patent applications for inventions involving microorganisms, plasmids, vectors, cells, plant tissues, seeds, and other biological materials that are not generally available or reproducible are often supported by a deposit in a recognized patent depository. A deposit is employed in many cases to meet the requirement that a patent provide 'enablement' or the best mode of practicing an invention.

The PTO first published guidelines on the deposit of microorganisms in 1971. In 1977, establishment of the Budapest Treaty required contracting States that allow or require the deposit of microorganisms as part of their patent procedure to recognize the deposit of a microorganism with any International Depository Authority. In 1985, the Court of Appeals for the Federal Circuit held that the enablement provision of the patent statute did not require a deposit in a recognized depository by the filing date of the patent application, but only before the issuance of the patent. In 1988, the PTO published proposed rules for deposit of biological materials for patent purposes. These rules, if adopted formally by the PTO, will assist the inventor and the depository in defining the position of the PTO on deposits.

The new patentable status of animals raises the possibility that the PTO will encourage or require the deposit of animal forms to support certain patent applications. To date, no animal has been deposited with a depository. In the case of the first animal patent granted (U.S. 4,736,866), the deposit requirement was satisfied not by deposit of a mouse or other animal, but by deposit of the DNA plasmids bearing the cancer-causing genes intended for transfer into an animal. In the patent, the inventors provide detailed instructions for inserting those genes into mouse embryos to produce transgenic mice.

The patenting of animals could be problematic if deposit of the animal is required. Currently no depository is willing to accept the deposit of animals because the cost of facilities and expertise needed to maintain animals would be prohibitive. A depository maintaining animals for patent purposes might be subject to adverse publicity. If it were necessary to maintain the animal, a depository might need to grow another sample to prove the replication of the animal. After growth of the animal, disposal might not be acceptable and, therefore, maintenance of progeny would be necessary. It is not clear how a depository would make samples of an animal available or how it would create more animals. Maintenance of many kinds of short-lived animals for the current required period of 30 years would not be possible.

The deposit of animal embryos may not present the same difficulties as long as the embryos can be successfully frozen and recovered. To date, at least 13 species of animal embryos (cattle, mice, rats, rabbits, hamsters, sheep, goats, horses, cats, antelopes, and three species of nonhuman primates) successfully have been frozen and recovered.

INTERNATIONAL PROTECTION FOR PLANTS AND ANIMALS

Intellectual property protection of microorganisms, plants, animals, and biological processes is of increasing concern to the world community. International patentability is one element of the current debate in the United States regarding the scope of patentable matter. For example, those who favor patenting of animals point out other countries that either permit or do not expressly exclude the possibility of such patents. Opponents of patenting of animals can point to other nations that expressly exclude or have yet to issue patents on animals.

Several international treaties and agreements relevant to biological inventions seek to harmonize various procedural and substantive elements of international patent practice. However, the patenting of animals is not the subject of any existing treaty. Of the existing agreements, the European Patent Convention (EPC) is most relevant to the substantive issue of patenting plants and animals. Article 52(1) of the EPC defines patentable subject matter as inventions that are susceptible to industrial application, are new, and involve an inventive step. This definition is extraordinarily general. Rather than providing a precise, positive definition of patentable subject matter, the EPC instead narrows this broad definition by explicitly specifying negative restrictions. One such exclusion is article 53(b), which stipulates that European patents will not be issued for plant or animal varieties and essentially biological processes for the production of plants and animals (with the exception of microbiological processes or the products thereof): Although plant varieties are specifically excluded, there is no general exclusion for plants. According to the Technical Board of Appeal of the European Patent Office (EPO), article 53(b) of the EPC prohibits only the patenting of plants that are in the genetically fixed form of a plant variety, i.e., a specific variety such as the rose "Peace" or the wheat cultivar "Chinese Spring. " Thus, EPO will grant utility patent protection for a plant that has had a gene inserted (e.g., corn having gene X), if it is not a specific plant variety (e.g., corn inbred A having gene X). Similarly, a process for transforming a plant to insert a desired gene would be patentable because human intervention played a greater role in the final result than biological forces. This viewpoint has been adopted by the Swiss Patent Office as well as by the European Patent Office, which in early 1988 granted a patent on a technique for increasing the protein content of forage crops such as alfalfa and for the plants produced with the aid of the technique. This decision arguably opens the door for plant and animal patenting in Europe, subject to the specific treatment of European patents on a country-by-country basis.

Differences do exist between nations regarding intellectual property protection of biotechnological inventions, including the issue of what constitutes patentable subject matter. Patent protection is widely available for microorganisms, as are various forms of patents and breeders' certificates for plant life. Analysis of the laws of other nations indicate that patent protection on animals is permissible or theoretically possible in a number of nations. Any projection of the number of nations permitting animal patents must be speculative in the absence of additional activity in this area. To date, only the United States has announced a policy permitting patents on animal life forms and issued a patent on an animal invented through biotechnological techniques. It is likely that other nations will issue such patents in the future. The Japanese patent office, for example, recently issued an internal notice announcing its intention to grant patents on nonhuman animals if they meet the requirements of their patent law.

ISSUES AND POLICY OPTIONS FOR BIOTECHNOLOGY

Intellectual property is one of the most important assets for a company attempting to commercialize biotechnology-related processes and products. Patents often are used by start-up companies to lure crucial financing and to gain access to new markets. Patent protection has played a major role in the development of biotechnology-based pharmaceuticals. Patents and other forms of intellectual property (plant breeders' rights, trademarks) are similarly important to the commercial development of a range of agricultural products.

Under United States law, patents may be issued for any new, useful, unobvious process, machine, manufacture, composition of matter, or new and useful improvement of these items. Under this broad umbrella, U.S. law has permitted the patenting of micro-organisms, plants, and nonhuman animals. The patenting of nonhuman animals has led to legislative debate regarding whether such patents should be granted. Options for congressional action—including discussion on issues such as deposit con-

siderations and exemptions from infringement for certain classes of users—were presented in an earlier OTA report (New *Developments in Biotechnology: Patenting Life)* and are incorporated here by reference (10).

In terms of the breadth of patentable items, U.S. patent law is the most inventor-friendly statute in the world; it is unique in that it makes no exceptions to patentability found in the statutes of many other countries (e.g., animal and plant varieties, public order or morality, products such as pharmaceuticals, and foods). If Congress takes no action regarding patentable subject matter, broad protection for inventions created by biotechnology will continue. Laws created by Congress to regulate interstate commerce would be relied on to govern the development, approval, sale, and use of such inventions. Congress could, either through moratorium or prohibition, specifically bar patents from issuing for nonhuman animals or human beings. Such action would clarify congressional intent regarding the limits of subject matter protection, but it would also create a precedent of using patent law, rather than laws regulating commerce, to discourage certain types of inventions.

To date, only one patent on an animal has been issued. Since this occurred (1988), no further patents have been issued, and the backlog of such patent applications now numbers over 160. Since the status of specific patent applications is, by law, confidential, there is no way to ascertain when, or if, the PTO will issue subsequent animal patents; and further, if issued, whether such patents will have agricultural applications. Congress could, through its oversight powers, ask PTO to explain the present status of such patent applications.

The need to harmonize U.S. patent law with the laws of other nations is likely to come to Congress' attention as a result of several ongoing efforts: the General Agreement on Tariffs and Trade (GATT), the World Intellectual Property Organization (WIPO), amendments to the Union for the Protection of New Varieties of Plants (UPOV), and other bilateral and multilateral trade discussions. It is too early to predict specific options arising from each of these forums. In all cases, the goal of harmonization should be the creation of consistent laws addressing substantive and procedural issues in patent practice.

INTELLECTUAL PROPERTY PROTECTION AND COMPUTER SOFTWARE

As with biotechnology, the merging of intellectual property law and computer software represents the joining of old law with new technology. Computer software can be protected under copyright, patent or trade secret law, or some combination of these. This section briefly reviews these forms of protection for computer software and discusses some issue areas for agricultural software use.

Copyright

The current copyright law is enacted in the Copyright Act of 1976, as amended. A 1980 amendment made explicit provisions for computer programs as (literary) works of authorship (P. L. 96-5 17). Copyright protects ''original works of authorship' from unauthorized uses including reproduction (copying), making derivative works (adaptation), public distribution, public performance, and display. Generally, the term copyright for new works is the life of the author plus 50 years, or 75 years for works made for hire (e. g., by an employee of a firm).

Copyright has been the form of software protection favored by most nations and will be the most widely used for agricultural software. Obtaining a copyright is easy, inexpensive, and quick compared to the requirements for a patent. And since a copyright is administered under Federal law, unlike trade secret protection, it is uniform in all the states. The duration of copyright protection is very long, compared to the expected economic or technical lifetimes of computer programs.

The doctrine of fair use is one of several statutory limitations on copyright holders' exclusive rights. Under this doctrine, certain unauthorized uses, such as copying for the purposes of teaching, scholarship, or research, may be considered ''fair use, '' not copyright infringements. Whether an instance of copying is a fair use instead of an infringement is determined by the courts.

Another statutory limitation on the rights of software copyright holders is contained in the 1980 amendment. It states that it is not an infringement for the owner of a copy of a computer program to make or authorize the making of a copy or adaptation of that computer program provided that such new copy or adaptation is created as an essential step in utilizing the program or that it is for archival purposes only and that all archival copies are destroyed in the event that continued possession of the computer program should cease to be rightful. This limitation clarifies the right of a user who legitimately owns a software product to make "backup' copies of the software to protect against damage or loss, to load the software onto the hard disk of a computer for easier or more efficient use, and to make any necessary adaptations to make the program usable on a computer. It does not

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

There is disagreement over what features of a computer program are copyrightable. The distinction between idea and expression can be difficult to determine.

permit, for example, the making and distributing multiple copies for school or office use.

Copyright does not confer rights over ideas—only the expression of an idea is protected, not the underlying idea itself. This could be considered a disadvantage by the software developer because the copyright will not preclude a competitor from creating a new work embodying the same idea, so long as the competitor does not incorporate copyrighted expression from the first program into the second program. For software, copyright may also allow reverse engineering practices. This means that one team of software developers studies the code of a copyrighted program to extract the underlying ideas. A second team then creates a new program, based on the first team's functional specifications. The extent to which these are protectable expressions, as opposed to uncopyrightable ideas, is the focus of recent court cases.

Considerable disagreement exists over what features of a computer program are copyrightable. The distinction between idea and expression can be quite difficult to determine, even for some traditional literary works like books and plays. For software, which is intrinsically functional, idea and expression are closely interwoven. It is difficult to separate which elements of a program are the expression and which are the underlying idea. There is substantial disagreement among legal scholars and among software developers and computer scientists as to whether copyright should protect only against literal or near-literal copying or should also protect a program's structure, sequence, and organization and user interfaces as well. For example, some argue that a program's ''look and feel" (e.g., computer program screen displays) should not be protected by copyright;[1] instead protection for "look and feel" is better suited by a patent. Others are critical of the patent protection for computer programs (1 1).

Patent

As discussed earlier, a patent protects an invention including the expression of an underlying idea, from copying and from independent creation for a period of 17 years. It protects against literal infringement (making, using, or selling the claimed invention) and also against infringement by equivalent inventions, whether or not the infringing inventor had prior knowledge of the patented invention. The subject matter of a patent is limited to a process, machine, article of manufacture, or composition of matter that is novel, nonobvious, and useful, or to new and useful improvements to these classes of patentable subject matter. However, the following generally cannot be patented: ideas, scientific principles, phenomena of nature, and mental processes. For a knowledge-based system, obviously it may be difficult to patent the knowledge in the system if it is common knowledge associated with the profession (4), Patents probably will be of little value to applications of advanced computer technologies, although they should be of value to a basic computer scientist who develops domain-independent tools (e.g., inference engines).

The requirements for a patentable invention are relatively stringent; patents do not reward hard work per se.

[1] Courts have addressed copyright issues in disputes relating to computer program screen displays, distinguishing **copyrightable** expression **from unprotected elements** in the text, menu hierarchies, command structure, key sequences, and other aspects of a program's ''interface' with the user (12).

The patent requirements for novelty and nonobviousness are more difficult to satisfy than the ''originality' criterion of copyright. (All "original" software is eligible for copyright, as with any other work of authorship, and copyright inheres in a work as soon as it is created.) Although patents are being granted for software-related inventions, only a small fraction of these inventions is likely to contain a computer process meeting the tests of novelty and nonobviousness.

An advantage of patent protection for the discoverer of a software-related invention is that the patent will protect all the claims for the invention as a whole. In contrast, many of the processes underlying a software invention would likely not be protectable under copyright because they would be considered part of the unprotected ''idea. A single computer program may consist of a number of patentable processes and algorithms. At the same time, the claimed invention might be executed by a number of copyrighted programs. Depending on how carefully claims are constructed, the computational logic and processes and even the algorithm itself can be patent protected.

The availability of patent protection for software-related inventions was unclear until the early 1980s. During the 1980s patents were issued for software-related inventions such as linear-programming algorithms, spell-checking routines, and logic-ordering operations for spreadsheet programs.

Some patent lawsuits concerning software-related inventions and controversies concerning patents for algorithms became highly visible in the late 1980s. These lawsuits have focused concerns over the appropriateness of patent protection for software-related inventions and algorithms. Some argue that patents on computer-program processes do not encourage technological progress and point to the practical problems of administering the patent system for software-related inventions.

One such problem is the incomplete "prior art" available to patent examiners in evaluating patent applications for processes involving computers, especially those involving software and algorithms. [2] The published literature does not completely represent developments in the fields of software and computer science. In many cases, important prior art exists only in product form and is not described in print form such as articles in technical or scientific journals. Another problem is the lack of special classifications or cross-references to issued patents. As a result, it is virtually impossible to find, let alone count or profile, all software-related patents. Thus, patent examiners have no effective way of searching and studying such patents.

Another problem is the long time lag between patent application and issuance, compared to quick-moving software life cycles. Patents under examination are not disclosed, so a competitor may put considerable effort into developing a program that unknowingly duplicates computer processes for which one or more patents are pending. Finally, the process of obtaining a patent is expensive and lengthy, compared to copyright or trade secret protection. Although turnaround time in the Patent and Trademark Office (PTO) is decreasing, a patent still may take years to issue in an industry where products have short economic lifetimes (11).

Trade Secret

Trade secret protection, provided under individual State laws, protects against use or willful disclosure of trade secrets by others, but does not penalize independent discovery. Unlike copyright or patent, there is no limitation on its duration. Trade secret has been the most-used form of protection for mainframe and minicomputer software. Its main advantages are that it protects a program's underlying ideas, logic, and structure, not just expression as in copyright. Trade secret avoids formalities of registration or application and lengthy waits for protection. Enforcement is straightforward and injunctions or compensatory relief is available for those who can prove misappropriation of trade secrets.

Trade secret protection, however, does not protect against independent creation, reverse engineering, or accidental disclosure of the secret. For software protection it is relatively weak and is best used in conjunction with a copyright or patent (7). It can also be costly or impossible to maintain secrecy. Finally, the lack of uniformity in State laws can be frustrating.

If software is protected by trade secret, it maintains that status so long as it is not publicly disclosed. This can stifle the spread of knowledge about software state-of-the-art and in turn can adversely affect knowledge of prior art for patent examinations as discussed earlier (11).

[2] **Prior** art is **that which is** known or **available** to a person skilled **in the relevant** field of technology. **Evidence** of prior art **(e. g., existing patents,** publications) is **evaluated** not only for what **it** expressly **teaches, but** also for what **it** would **fairly suggest** to one of **Ordinary** skill **in the relevant field** of technology **(I I).**

oto credit: Steven Bent

software inventions have become highly visible. A concern is the incomplete "prior art" available to patent examiners.

INTERNATIONAL PROTECTION FOR COMPUTER SOFTWARE

The United States is a major international competitor in computer software development and sales. In 1987, about 40 percent of the U.S. software developers' revenue came from foreign sales (13). Many multilateral and bilateral treaties help protect the intellectual property of software developers through patent and copyright.

Copyright is the predominant form of software protection in the United States and abroad. In most countries, computer programs per se are not eligible for patent protection. However, in some countries, including the United States, certain types of computer-implemented processes and algorithms can be patented.

Copyright and patent protections abroad are very similar in form to those in the United States and have most of the same advantages and liabilities. Copyright protection abroad is provided principally through the Berne Convention and the Universal Copyright Convention. The United States joined the Berne Convention in March 1989. The treaty was first established in 1886 and is the primary multilateral agreement in the world dealing with copyright.

The United States is also a member of the Universal Copyright Convention (UCC), which was established and adopted by the United States in 1955. UCC provides less protection than the Berne Convention and has lower minimum standards. In nations that agree to both Berne and UCC, Berne takes precedence.

The Berne Convention is recognized in 79 nations, and gives U.S. software developers protection in 24 countries where there was no previous copyright agreement. The United States has bilateral agreements with 33 nations as well, often in addition to common Berne or UCC membership. The procedures are simple: once a copyright exists for a work in a member nation, it applies in all signatory nations, according to their own laws. Computer programs are not specifically mentioned in either convention, but are commonly acknowledged to be included.

Securing patent protection in foreign countries is a difficult process. Patents for any invention are difficult to obtain due to the rigorous standards of novelty and nonobviousness. A patent must be applied for in each country where it is to be valid—there is no universal patent process.

in most countries, software per se is not considered patentable. The United States is a member of the oldest and most extensive patent treaty, the Paris Convention, established in 1883. There is no requirement in the Convention that software-related inventions be considered patentable.

Trade secret has been the traditionally favored method of protection for mainframe and minicomputer software developers in the United States. However, most countries outside of the United States and Western Europe do not recognize either domestic or international trade secret protection. No international conventions for trade secret exist.

International standards for intellectual property law are important to encourage and to protect U.S. inventions. The United States is attempting to include intellectual property in the General Agreement on Tariffs and Trade (GATT) treaty and is engaged in bilateral negotiations as well (11).

ISSUES AND POLICY OPTIONS FOR COMPUTER SOFTWARE

Copyright and Patent Issues

Rapid technological advances in computer software are challenging the intellectual property laws in the United States and internationally. Copyright law offers straightforward remedies for the literal copying of program code, although enforcement remains a problem. especially overseas. Functional aspects of computer programs pose difficult questions for the application of copyright. The traditional "fuzzy" line between idea and expression in copyright is confounded by the need to determine an appropriate scope of protection in light of the intent of current law.

The protection of software-related inventions by patent is a fairly recent and controversial development. The PTO faces considerable challenges in examining applications for computer-related inventions. PTO has an incomplete data base of ''prior art' for computer-related inventions. Much of what constitutes prior art historically has been in the form of products, not literature or issued patents. This makes it very difficult for examiners to judge whether an application describes a "novel" and ''nonobvious' invention. Improving electronic search and retrieval capabilities for PTO's own database is critical since it is used by the patent examiners during the application process. Currently, PTO is unable to provide statistics on the number of patents issued for software-related inventions except through time-consuming man-

ual search, review, and selection from various large patent subclasses (12).

Options for congressional action are presented in the OTA report *Finding A Balance: Computer Software, Intellectual Property and the Challenge of Technological Change* and are incorporated here by reference. If Congress chooses not to act, the status quo is maintained but uncertainty as to how current intellectual property law applies to computer software remains. On the other hand, taking action may reduce some uncertainties but add others, especially if additional bodies of case law or international agreements have to be developed. If Congress chooses to take action, it must decide how comprehensively to act. Actions might take the form of measures to address ongoing institutional problems (e.g. prior art and examination quality issues facing PTO) or legislative measures to amend current copyright and patent statutes or to create *sui generis* (of its own kind or class) protection. Generally, congressional action might

1. explicitly affirm the status quo and course of case law;
2. make small adjustments at the margins of copyright and patent law possibly through procedural changes;
3. clarify or modify the scope of patent or copyright but leave the basic paradigms unchanged;
4. introduce one or more *complementary, sui generis* protection tailored specifically at certain aspects software innovation; and
5. develop *sui generis* protection to *substitute* for copyright and/or patent protection.

(See the above referenced OTA report for a discussion of the issue areas in the context of these choices.)

Liability Issues

It has been said: "To make a mistake is human, but to really mess things up requires a computer. Unfortunately, mistakes can occur in using advanced computer technologies, and some mistakes can lead to personal injury or financial loss. The liabilities associated with such ''torts'' need to be examined. This issue is not specific to agriculture but applies to the computer industry in general.

The issue of personal injury arises in areas such as medicine where a computer application is controlling a patient's treatment (e.g., the level of radiation in cancer treatment) but is unlikely to arise in business applications such as agriculture. Therefore, the main concern will be with financial loss as a result of bad advice (4).

To recover in negligence, the plaintiff must show that the defendant did not take sufficient care in developing the system to prevent injury (4). The courts have not established standards for adequate care, but developers would be advised to maintain detailed records of knowledge sources, verification tests, and validation procedures. Inclusion of a disclaimer at the beginning of each program has been suggested to insulate the developer from such litigation. Gemignani (4) suggests the following:

> **SOFTWARE IS INTENDED TO BE USED BY LICENSED PROFESSIONALS ONLY. THE USER ASSUMES SOLE RESPONSIBILITY FOR DECISIONS CONCERNING ADVICE OR TREATMENT. IF YOU DISAGREE WITH THIS POLICY, YOUR LICENSE FORBIDS YOU TO USE THIS SOFTWARE**

The issue of liability has not been a major problem in agricultural computer applications, possibly as a result of the small amount of activity in knowledge-based systems. However, it is a topic frequently mentioned among program developers. Stressing the view that these are decision support systems that provide advice to professionals is important. In this light, such systems are similar to a colleague who provides advice.

A related issue in software development is the lack of regulation. Software must conform to standard regulations (e. g., patents, fraud, etc.) but need not be approved by any Federal agency. The medical field is a potential exception. The Food and Drug Administration proposed reviewing software that is the component of a medical device or that is used in the clinical management of patients. Therefore, it is likely that software that claims to make medical decisions will be regulated (4). Government regulation is unlikely to protect a developer from negligence claims; however, it may relieve some of the paranoia that exists among developers.

User Issues

When advanced computer technologies are developed, they will be available to agribusiness professionals and agricultural producers. An interesting negligence liability issue may exist if the consultant making the recommendation to a producer chooses not to use an available technology (4). The argument stems from an historic case where a tugboat lost the barges it was towing in a storm. The situation might have been avoided if the tugboat had a radio on board. The owner of the tugboat was held liable because of failure to use an available technology—even though radios were not yet standard equipment on

tugboats. According to this case, three criteria must be proven to establish negligence in not using a technology:

1. The technology must be readily available.
2. The technology must be reliable.
3. The cost of using the technology must bear a reasonable relationship to the harm that might be suffered in the absence of the technology.

Thus far, this precedent has not been tested with computer technologies. However, this suggests that for those who advise farmers, such as Extension agents, consultants, input suppliers, processors, etc., they may be obligated to adopt these technologies.

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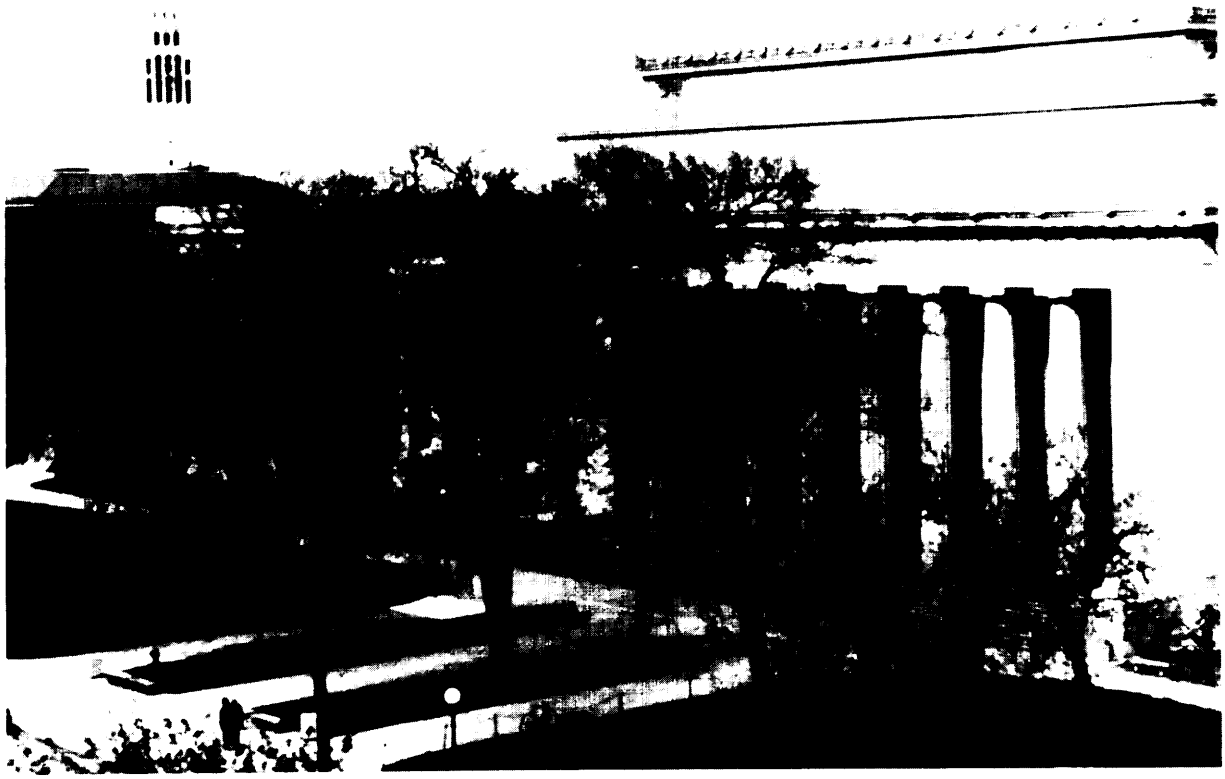
Chapter 16

Institutional Change Within the Land-Grant System



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The U.S. agricultural research system is large and diverse, employing some 23,000 doctoral level agricultural scientists and economists in academia, industry, and government. For many years, funding of agricultural research was divided evenly between the public and private sectors, but recent studies indicate that today this is not the case—nearly 60 percent of the funding for agricultural research is in the private sector **(9).**

The public-sector agricultural research budget exceeded $2.2 billion for 1989; Federal funding for agricultural research, however, has been a shrinking proportion of total Federal research funding. In 1955, for example, the research budget for the U.S. Department of Agriculture (USDA) represented 13.4 percent of the total Federal nondefense research funding, but was only 4.6 percent of the funding in 1988 (7).

The public agricultural research system nonetheless plays a significant role in the American economy. Studies have estimated high rates of social returns to public agricultural research investments, indicating that these investments have been a wise social investment.

Different types of research are conducted by the public and private sectors and is determined by the extent of externalities. Externalities exist when the action of a single entity (or firm) affects the environment (or decision) of another. If they exist the private sector cannot capture the full returns of its investment, and will not invest in such research at socially optimal levels. The public sector must fill in the gap. The private sector, for example, conducts little agriculture-related social science research; primarily the role of the public sector. Research that creates easily transferable information is conducted by the public sector, while research that creates information embedded in a product is conducted by private sector. For example, the public sector develops pure lines and self-pollinated crop varieties that can be used by any seed company while the private sector develops hybrid varieties that must be purchased annually by farmers if they are to be productive.

The U.S. public sector agricultural research system, a dual Federal-State system, had its origins in the 1860s, but it was not until the late 19th century that the system truly began to acquire the capacity to provide the scientific knowledge needed to deal with the problems of agricultural development. Today the Federal agricultural research system includes the USDA's Agricultural Research Service (ARS), Economic Research Service (ERS), and Forest Service; and the State Agricultural Experiment Stations (SAES) located within the land-grant university system.

The Agricultural Research Service, established in 1953, conducts basic and applied research in six programs covering Natural Resources, Plant Science, Animal Science, Commodity Conversion and Delivery, Human Nutrition, and Integration of Systems. ARS employs approximately 2,670 scientists and engineers (of which about 2,500 have doctoral degrees) and had a fiscal year 1991 research budget of $624 million. Research is conducted at some 127 domestic and 7 foreign locations, including 5 major regional research centers located in Maryland, Pennsylvania, Illinois, Louisiana, and California. ARS has cooperative research agreements with other USDA agencies and many of the ARS facilities are located at or near academic institutions. Some ARS staff hold adjunct faculty appointments and participate in graduate teaching (7, 17, 18).

The Economic Research Service was established in 1961 to provide economic and other social science information and analysis for improving the performance of agriculture and rural America. ERS collects and maintains a number of historical data series on farm type, size, and number; production and input levels; trade; effects of farm policy; and socioeconomic characteristics of rural areas of the United States. The ERS also performs statistical and analytical research, and is organized into four divisions covering Commodity Analysis, Agricultural and Trade Analysis, Resources and Technology, and Agricultural and Rural Economy. ERS has limited funds to contract for research in the academic sector but is not authorized to administer a competitive grants program. The ERS budget for fiscal year 1990 was $51.3 million (7, 16).

The Forest Service is responsible for research on the Nation's forests and for technologies useful in the manufacture of pulp and wood-based products. Research topics cover a broad range, and the Forest Service also manages 182 million acres of forest. The research budget for fiscal year 1990 was $157.4 million.

The land-grant university system in the United States was established in 1862 with the passage of the Merrill Act. The impetus for establishing these land-grant schools arose from both a populist reaction to the elitism of uni-

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Table 16-1-Current Formula for Allocating Hatch Funds to States

- 20 percent of the funds are allocated equally to each experiment station.
- At least 52 percent of the funds are allocated as follows: ½ in an amount proportionate to each State's share of the total rural population of all States, and ½ in an amount that is proportionate to each State's share of the total farm population of all States.
- Not more than 25-percent of the funds are allocated to States for cooperative research in which two or more SAES cooperate to solve agricultural problems that are of concern to more than one State.
- 3 percent of the funds are for the administration of the Hatch Act.

SOURCE: National Research Council, Board on Agriculture, "Investing in Research: A Proposal to Strengthen the Agricultural, Food, and Environmental System, " National Academy Press, Washington, DC, 1989.

versities in the eastern United States, and a perceived need to provide higher education to the masses, with particular emphasis on the children of farmers and industrial workers. The Merrill Act made grants of land to States that were willing to create universities that would fulfill this mission. Originally, education focused on agriculture and the mechanical arts, but subsequently the educational focus has expanded to include all of the major disciplinary fields.

The partnership between the State and Federal Government was extended to research with the Hatch Act of 1887, which provided Federal funding for the support of agricultural experiment stations at land-grant universities. Before this, agricultural science was limited to the activities of innovative farmers and inventors and the industrial sector, and progress came primarily in the form of mechanical technology. Few States provided significant funding for agricultural research. Eventually, however, agricultural output did not keep up with demand and food prices began to rise. This set the stage for the passage of the Hatch Act. It was not until the 1920s that the land-grant system was fully functional. Today, there are 57 experiment stations located in each of the 50 States, the District of Columbia, the Pacific Territories (American Samoa, Guam, Micronesia, and the Northern Mariana Islands), the U.S. Virgin Islands, and Puerto Rico. Additionally, six historically black universities (the 1890 Universities) and the Tuskegee Institute also conduct publicly supported agricultural research (10).

The Hatch Act provides research funding to States based on a formula that considers the importance of the agricultural sector to the State's economy. The formula funding system (table 16-1) provides stable funding for research programs that may have long gestation periods. All formula funds must be matched by the State. The current formula for funding designates 1955 as the base year and the minimum amount to be allocated.

The structure of the current system was completed with the passage of the Smith-Lever Act in 1914, which created the Cooperative Extension Service-a mechanism to carry the results of the research system to the farmer. Funding is provided by a formula mechanism somewhat similar to that of the Hatch Act. Today there are extension offices in nearly every county in the United States, employing approximately 9,650 county agents and 4,650 scientific and technical specialists; the extension budget totals about $1.2 billion annually (31% Federal) (13).

THE MISSION OF LAND-GRANT UNIVERSITIES

Land-grant universities are distinguished from other universities by their legislatively mandated mission; the Federal-State partnership embodied in the formula funding mechanism; and their integration of research, teaching, and extension. Academic departments within the State Experiment Stations have three functional budgets, one each for teaching, research, and extension; individual professors tend to have joint appointments in one or more of these functional endeavors.

The legislated mission of the system is to provide higher level education to the masses; apply research knowledge to the solution of society's problems; and provide outreach or extension programs for nonresident instruction groups. Over time, the sense of institutional mission has declined as research has become more basic and more focused on increasing disciplinary knowledge than on solving the problems of society. Less emphasis has been given to the development and adaptive research needed to apply basic research to solving social problems. When the system was first established, disciplinary specialization had not yet progressed very far; it was easy to obtain multidisciplinary cooperation among scientists and to communicate the research results to lay people. This is no longer the case.

Rapid post-World War II advances in knowledge and increasing intellectual specialization has made interdisciplinary cooperation and extension increasingly difficult. Specialized language, compounded by the scientific illiteracy of the public, has increased the difficulties in communicating research results to the public. This situation will be even more problematic for research conducted with the tools of biotechnology. The lack of

understanding of these technologies has raised public concerns and in some cases a call for the end of this type of research. University researchers will need to improve their communication skills with the public if they wish to enjoy the academic freedom to conduct this research. The basic premise that the same faculty can efficiently fulfill the multiple missions of the modem land-grant university (research, teaching, and extension) still prevails, but tensions are growing in the system as it becomes more and more difficult to achieve these multiple ends.

The research system must have public support and funding to function. It also must have the flexibility to reallocate scarce resources to new priorities, and to attract highly qualified personnel that can keep abreast of changing technological opportunities. Despite high social returns to public sector agricultural investments, the system has been the subject of criticism from internal and external sources. External critics focus primarily on the heavy research emphasis on agricultural productivity and the lack of research devoted to nutrition, rural problems, and environmental concerns. Internal criticisms have focused on the perceived low quality of the research, on the inadequate interaction of agricultural researchers with the basic scientific disciplines that underlie agriculture, and on the limited role of peer evaluation in project formulation and review. In addition, public-sector budget constraints have frozen funding. Thus, the public sector agricultural research system is being challenged from many directions. Whether the system can be revitalized and renew its historical commitment to solve the problems of society, or whether it becomes isolated and loses its credibility with the public remains to be seen. The decade of the 1990s will be a period of significant change within the agricultural research system.

CHANGING ENVIRONMENT FOR AGRICULTURAL RESEARCH

The ability of the land-grant system to carry out its historic missions is becoming increasingly suspect. Internal as well as external pressures could significantly alter the structure and function of the system. Changing political support, resource base, and institutional frameworks combined with the development of revolutionary new technologies will put presure on the system to change dramatically.

The Political Environment

Historically, political support for the agricultural research system has come primarily from the farm and rural population; as a result, agricultural research has placed heavy emphasis on increasing the productivity of agriculture. However, agricultural's traditional base of support has been eroding steadily. Farm numbers and populations have been declining (table 16-2), and today more than 75 percent of the total U.S. population resides in metropolitan areas. Of the 435 members of the House of Representatives, approximately 100 represent rural districts and this proportion will decline with the new redistricting in 1992 (12).

Table 16-2—Number of Farms in the United States, Selected Years

Year	Number of Farms
1900	5,737,000
1950	5,382,000
1960	3,963,000
1970	2,949,000
1980	2,433,000
1984	2,328,000
1986	2,214,000
1989[a]	2,172,920

[a] *1989* figures are preliminary.

SOURCE: U.S. Department of Agriculture, *Agricultural Statistics,* Washington, DC, various years,

Public interest groups have become increasingly critical of the emphasis on productivity in agricultural research. *Silent Spring (1)* and *Hard Tomatoes, Hard Times (3)* criticized the system for its failure to consider the problems of rural communities, the environment, and consumer needs. Environmental, consumer, and animal welfare groups have become increasingly active in the debates of recent Farm Bills. Additionally, these groups have challenged the universities themselves by bringing forward law suits on the use of public funds for productivity increasing research. For example, a law suit was brought against the University of California system for the development of a mechanical tomato harvester.

The changing demographics of the United States combined with the increased activism of a wider range of constituents is indeed changing the climate in which the land-grant system conducts research. The 1985 Farm Bill contained several conservation measures, and many more such measures were added in the 1990 Farm Bill. Several environmentally oriented research initiatives, such as the groundwater initiative and the low input sustainable agricultural initiative were also passed. Congress increasingly has earmarked agricultural research funds to help the agricultural research system more quickly to adjust to these new priorities. (See table 16-3.)

The political climate is changing at the State level as well, as State agricultural income dwindles. In 1980,

Table 16-3-State Agricultural Experiment Station Funds From Special Grants, Selected Years
(in millions of dollars)

Year	Special grants
1982	12.9
1984	15.8
1986	19.9
1987	21.8
1988	23.2
1989	29.1
1990	39.6

SOURCE: Cooperative State Research Service, Inventory *of Agricultural Research,* **U.S. Department of Agriculture, Washington, DC, various years.**

nearly 29 percent of nonmetropolitan counties received at least one-fifth of their total income from farming-related industries. That number had dropped by 1986 to 21 percent and it continues to decline (2). During past recessions, State support for the land-grant system generally has remained strong, but during the last 2 years, as State budgets have become severely constrained, support for the land-grant system has wavered. Not only is funding not increasing, in many States it is actually declining. Thus, for the first time since World War 11, the University of Minnesota received a cut in its operational budget; faculty salaries were frozen for 2 years. Additionally, proposals were introduced in the State legislature to have students pay the full cost of their resident instruction (11). Other State universities are facing similar situations.

The Resource Base

Although total research funding for the State Agricultural Experiment Stations (SAES) has increased slightly over the last decade (table 16-4), in general agricultural research is underfunded. The States provide the majority of the funding for research at the SAES, and through the 1980s, State support increased by 58 percent. (See tables 16-4 and 16-5.) However, the recession of the early 1990s has constrained State budgets, resulting in few increases and in some cases declining State support for agricultural research.

The USDA is the second largest single contributor to SAES research funding. Historically, USDA funding has been in the form of a block grant formula funds. Decisions concerning allocation of these funds have been made at the local level. USDA funding has basically stagnated and barely keeps up with inflation. Increases in USDA funding primarily reflect congressional earmarking of special grants for such areas as water quality, nutrition, and integrated pest management and biological control research.

In response to widespread criticisms of the agricultural research system, a major new funding initiative was undertaken in 1977 to establish a USDA competitive grants program. Competition for funding is open to researchers from both the land-grant and non-land-grant universities and research laboratories. Today, grants are awarded in plant and animal systems; natural resources and the environment; human nutrition, food quality, and health; markets, trade, and policy; and development of new products. Funding for the program was $15 million in 1978, rising to $39.7 million in 1989. Partly as a result of a National Research Council proposal to strengthen agricultural research, allocations of the competitive grant program rose to $97 million for 1992. However, funding per grant is small relative to other Federal agency grant programs.

Researchers within the SAES also can compete for competitive grants from other Federal agencies such as the National Institutes of Health (NIH) and the National Science Foundation (NSF). Competitive grant funding from such agencies to the SAES researchers and projects increased by 83 percent between 1982 and 1989, and now represents about 10 percent of total SAES research funding.

Funding from the private sector has increased by 60 percent since 1982 (table 16-5). Private sector funding comes from industry or from the sale of products by the university. Currently these sources of income represent less than 9 percent of the total funding. Analysts speculate that industry-supported research is not likely to continue growing at such a high rate, as many research-intensive industries are reducing their own in-house research budgets. However, funding likely will be available for selected research programs that are expected to yield high payoffs. The product sales category also is a potentially lucrative source of funding for universities. Legal and institutional changes, which will be discussed later in this chapter, have made it easier for universities to capitalize on their research. Income from product sales rose only 6 percent between 1982 and 1986, but increased 33 percent between 1986 and 1989.

Research funds are not evenly distributed to all experiment stations (table 16-6). The experiment stations in 12 States (California, Florida, Iowa, Illinois, Indiana, Michigan, Minnesota, North Carolina, Nebraska, New York, Texas, Wisconsin) account for nearly 49 percent of the total research funding available to the SAES, nearly 69 percent of the USDA competitive

Table 16-4-Research Funds for State Agricultural Experiment Stations, Selected Years[a]
(in millions of dollars)

Year	USDA[b]	USDA competitive	Other Federal[d]	State[e]	Industry	Product sales	Other[f]	Total
1982	161.3	5.5	77.8	522.2	57.0	58.5	70.0	952.3
1984	174.9	6.1	81.7	591.4	64.1	61.3	79.8	1,059.3
1986	174.4	11.9	110.8	704.3	78.1	62.9	89.8	1,232,1
1987	175.6	16.8	114.9	732.5	87.4	68.4	104.2	1,299.8
1988	187.0	19.3	115.0	770.0	91.2	77.8	114.1	1,374.2
1989	194.0	21.9	130.4	827.6	101.2	82.4	132.1	1,489,6
1990	203.6	20.0	143,9	877.9	113.8	91.6	145.7	1,596.5

[a] Funds are for State Agricultural Experiment Stations only and do not include the 1890 universities, the Schools of Veterinary Medicine, or the Forestry Schools. Funding is in current dollars.
[b] USDA includes Hatch, McIntyre-Stennis, Special Grants, Evans-Allen, Animal Health, and miscellaneous other funds administered by the Cooperative State Research Service.
[c] USDA competitive is the USDA competitive grants program.
[d] Other Federal includes funding from Federal agencies excluding USDA and includes funding from NIH, NSF, AID, DOD, DOE, NASA, TVA, HHS, PHS, etc.
[e] State is State appropriations.
[f] Other includes funding from nonprofit organizations, and contracts and cooperative agreements administered by USDA.

SOURCE: Cooperative State Research Service, Inventory of *Agricultural Research,* U.S. Department of Agriculture, Washington, DC, various years.

Table 16-5—Distribution of Research Funds by Source for State Agricultural Experiment Stations, Selected Years[a]
(in percent)

Year	USDA[b]	USDA competitive	Other Federal[d]	State[e]	Industry	Product sales	Other[f]	Total
1982	16.9	0.6	8.2	54.8	6.0	6.1	7.4	100
1984	16.5	0.6	7.7	55.8	6.1	5.8	7.5	100
1986	14.2	1.0	9.0	57.2	6.3	5.1	7.3	100
1987	13.5	1.3	8.8	56.4	6.7	5.3	8.0	100
1988	13.6	1.4	8.4	56.0	6.6	5.7	8.3	100
1989	13.0	1.5	8.8	55.6	6.7	5.6	8.8	100
1990	12.8	1.3	9.0	55.0	7.1	5.7	9.1	100

[a] Due to rounding, the total figure may not add to 100 percent.
[b] USDA includes Hatch, McIntyre-Stennis, Special Grants, Evans-Allen, Animal Health, and miscellaneous other funds administered by the Cooperative State Research Service.
[c] USDA competitive is the USDA competitive grants program,
[d] other Federal includes funding from Federal agencies excluding USDA and includes funding from NIH, NSF, AID, DOD, DOE, NASA, TVA, HHS, PHS, etc.
[e] State is State appropriations,
[f] Other includes funding from nonprofit organizations, and contracts and cooperative agreements administered by USDA.

SOURCE: Cooperative State Research Service, *Inventory of Agricultural Research,* U.S. Department of Agriculture, Washington, DC, various years.

grants, 61 percent of all competitive funds obtained from Federal agencies other than the USDA, and nearly 59 percent of all funding from industry support and product sales. The State Agricultural Experiment Station system clearly contains ''have and have not' institutions. The ''have not' institutions rely primarily on the traditional sources of funding (State and USDA formula funds), while the "haves" have diversified their funding sources.

The agricultural research system employs at least 23,000 PhD-level agricultural scientists, of which nearly 10,000 are employed in academia (table 16-7). Another 65,000 doctoral scientists who work in academia, may be conducting research applicable to agricultural problems. Of those research scientists employed in academia in applied agricultural disciplines, approximately 27 percent received their PhDs in fields other than applied agriculture. Sixteen percent received their doctoral degree in an agriculturally related basic science such as molecular biology, plant pathology, genetics, microbiology, and biochemistry, and 6 percent received their doctoral degrees in some natural science field such as mathematics, computer science, chemistry, or physics (table 16-8). Approximately 5 percent of academic researchers working in applied agricultural fields received their doctoral degrees in the social sciences and engineering. The percentage of academic agricultural researchers receiving their doctorate degrees in an agriculturally related basic science is lower than for agricultural researchers employed by other sectors of the economy.

Table 16-6—Research Funds for 12 Largest State Agricultural Experiment Stations, 1989

	USDA[a]	USDA competitive	Other[c] Federal	State[d]	Private[e]	Other[f]	Total
Total funding for 12 **SAES**[g] **($ million)**	**69.4**	15.0	80.0	399.8	107.5	58.0	724.6
Percent of total funding by source	9.6	2.1	11.0	55.2	14.8	8.0	100.0[h]
Percent of total SAES funding captured by 12 SAES	35.8	68.5	61.3	48.3	58.5	43.9	48.6

[a] USDA includes Hatch, McIntyre-Stennis, Special Grants, Evans-Alien, Animal Health, and miscellaneous other funds administered by the Cooperative State Research Service.
[b] USDA competitive is the USDA competitive grants program.
[c] Other Federal includes funding from Federal agencies excluding USDA and includes funding from NIH, NSF, AID, DOD, DOE, NASA, TVA, HHS, PHS, etc.
[d] State is State appropriations.
[e] Private includes industry support and product sales.
[f] Other includes funding from nonprofit organizations, and contracts and cooperative agreements administered by USDA.
[g] States include California, Florida, Iowa, Michigan, Minnesota, New York, North Carolina, Texas, Wisconsin, Indiana, Illinois, Nebraska.
[h] Due to rounding, the total figure may not add to 100 percent exactly.

SOURCE: Cooperative State Research Service, *Inventory of* Agricultural Research, U.S. Department of Agriculture, Washington, DC, various years.

Table 16-7—Doctoral Level Scientists by Employment Sector, 1985

Employment sector	Academia[a]	Industry[b]	Government	Total
Applied agriculture	9,900	7,000	**3,800**	**20,600**
Animal	2,500	1,100	**300**	**3,900**
Plant and soil	3,200	1,300	**800**	**5,300**
Food	700	1,800	**200**	**2,700**
Natural resources and environment	2,000	2,000	2,100	6,100
Other	1,500	900	300	2,700
Agricultural economics	1,900	300	400	2,700
Agricultural related basic science	31,300	**9,600**	5,000	45,900
Biological science	34,600	**10,700**	5,300	50,600

[a] Employment in academia does not include post doctorates.
[b] Employment in industry includes those who are self-employed.
[c] The distinction between basic and applied is somewhat arbitrary in that scientists employed in applied agricultural fields may be conducting basic research while those employed in agriculturally related basic science may be conducting applied research.

SOURCE: National Research Council, *Educating the Next Generation of Agricultural Scientists,* Washington, DC, 1988.

Table 16-8—Distribution of Applied Agricultural Scientists by Employment Sector and Doctorate Field, 1985
(in percent)

Field of doctorate	All sectors	Academia	industry	Government
Applied agricultural science[a]	61	73	50	50
Agriculturally related basic science[b]	20	16	22	24
Other natural Science[c]	13	6	8	10
Other[d]	6	5	8	10

[a] Appliecf agricultural sciences include animal breeding and genetics; animal husbandry, science, and nutrition; veterinary science; agronomy and soil; plant breeding and genetics; soil sciences; other plant sciences; horticulture and hydrobiology; food science and technology; fish and wildlife; forestry; environmental sciences; hydrology; agricultural engineering; and general agriculture.
[b] Agriculturally related basic sciences include biochemistry; biophysics and biometrics; ecology; cytology and embryology; molecular biology; genetics; bacteriology and microbiology; plant genetics; plant pathology; plant physiology; botany; immunology; nutrition and dietetics; animal physiology; and zoology.
[c] Other natural sciences include fields such as biological sciences notlisted above, health sciences, computer sciences, mathematics, chemistry, geology, physics, meteorology, etc.
[d] Other includes engineering; psychology, social scientists, humanities, and education.

SOURCE: National Research Council, *Educating The Next Generation of* Agricultural Scientists, Washington, DC, 1988.

Concerns have been raised that the physical plant of the universities has deteriorated. Many laboratories at **land-grant universities are old. Equipment, in many instances is obsolete and the cost of procuring new equipment to conduct new types of research,** such as biotechnology, is rising. This has been remedied to some degree by the development of research centers. In addition to providing an environment for multidisciplinary research, they allow for the sharing of expensive equipment and other laboratory needs for personnel conducting similar types of research. Such centers, however, are not the complete answer to this problem.

The Technology Base

To **continue** to perform high-level research, universities need to keep abreast of new information and technologies. New biotechnologies and information technologies in particular are yielding powerful research tools that can be applied to questions in a wide range of scientific disciplines. Effective use of these technologies will require new funding. or a reallocation of funding from traditional research projects. The scientists who use these new research tools will need a thorough grounding in the basic scientific disciplines that underlie biotechnology and information technology.

The allocation of resources (funding and research personnel) for research classified as biotechnology[1] at the SAES has been increasing (table 16-9). The primary funding sources for such research are USDA and other Federal agency competitive grants. and private industry (table 16- 10). It is likely that significant funds also arise from the licensing of technologies, royalties, and product sales.

The same 12 SAES that capture most agricultural research funds also are able to capture the majority of the resources devoted to biotechnology research (table 16-1 1). Indeed, the concentration of resources in only a few experiment stations is even more pronounced for biotechnology than for all agricultural research. Twelve experiment stations capture nearly 64 percent of all biotechnology funding available to the SAES and more than 65 percent of all competitive grant and private sector funding. These same stations also receive more than 72 percent of the "other" funds, which includes product sales. Additionally. the distribution of biotechnology funding by source differs for these 12 stations relative to the other SAES. They rely on competitive grants and private-sector funding for at least 40 percent of their biotechnology funding; only 17 percent of their total agricultural research funding comes from these sources.

Biotechnology research requires a thorough knowledge of agriculturally related biological and natural sciences. However, only about 16 percent of agricultural scientists working in academia received their PhDs in the basic disciplines underlying this new technology (i. e.. molecular biology. genetics, microbiology. etc.) (See table 16-8). Furthermore. most SAES do not include many of these more basic disciplines as part of the training of agricultural scientists. Thus, many agricultural researchers in academia lack formal training in the disciplines that underlie biotechnology. The same is true for advanced computer technology research.

Advanced computer applications have been used in agriculture for less than 10 years. Consequently, there is a shortage of scientists who understand and are capable of applying these technologies to agricultural problems. Existing personnel with these attributes are recently graduated PhD students and faculty who have taken a sabbatical leave to study this area, and they number less than 20 (4). Intensive training programs are needed to prepare researchers for the public and private sectors. Such training should consist of domain specific subject matter, computer science topics, and system design. Universities with identifiable agricultural programs in advanced computer applications include: Cornell University, Virginia Polytechnic Institute and State University. Purdue University, Texas A&M University, University of Illinois, University of Idaho, University of Kentucky, Pennsylvania State University, Mississippi State University, and North Carolina State University. However, each of these programs is narrowly focused.

The development of advanced computer technology relevant to agriculture is impeded by funding and a professional reward system in SAES that does not support the development of computer systems. Research in agriculture traditionally has been classical biological research whereby a researcher States a hypothesis and

[1] **Biotechnology is** first and foremost a set of tools and techniques. It is sometimes argued that resources are being shifted from other discipliner} activities into biotechnology research to the detriment of these other fields. Indeed, increased funding and scientist years (full-time equivalents) for biotechnology could mean that those resources are being taken away from other research programs. However, that is not the only plausible explanation. Because biotechnology is a tool, rather than an end in itself, increased resources for biotechnology}' research could also mean that the tools of biotechnology rather than traditional tools are now being **used** to examine the same questions. Thus, this research would now be classified as biotechnology even though the research focus is the same. A much more extensive examination of how biotechnology is being used is needed to determine if resources are actually being shifted from other disciplines into biotechnology'.

Table 16-9-SAES Resources Devoted to Biotechnology Research, Selected Years

Year	Projects	FTE[a]	Share of total FTE (percent)	Funds (million$)	Share of total funds (percent)
1982	**571**	**273.5**	**4.5**	**40.8**	**4.7**
1986	**1,043**	487.5	8.0	89.6	8.2
1988	1,360	681.9	11,1	131.3	10.6

[a]Full-time equivalent.
NOTES:Data is for 41 stationss responding to survey.
Stations not included are Alabama, Alaska, Connecticut, Delaware, District of Columbia, Idaho, Nevada, New Mexico, North Dakota, Pacific Territories, Virgin Islands, Vermont, Wyoming.
The 1984 survey was different from the other three and not completely compatible.

SOURCE: National Association of State Universities and Land Grant Colleges, Division of Agriculture, Committee on Biotechnology, "Emerging Biotechnologies in Agriculture: Issues and Policies," Progress reports I thru VIII, November, 1982–1989.

Table 16-10—SAES Biotechnology Research Funds, Selected Years

Year	USDA	USDA competitive	Other Federal	State	Private	Other	Total
			Funds by Source (in million dollars)				
1982	5.1	NC	14.6	16.2	4.9	NC	40.8
1986	0.6	7.1	20.9	38.0	9.5	3.5	89.6
1988	8.3	10.0	27.6	55.2	14.0	6.2	31.3
			Distribution of Funds by Source (as percent of total SAES biotechnology funds)				
Year	**USDA**	USDA **competitive**	Other **Federal**	**State**	**Private**	**Other**	**Total**
1982	12.5	NC	35.8	39.7	12.0	NC	100
1986	11.8	7.9	23.3	42.4	10.6	3.9	100
1988	13.9	7.6	21.0	42.0	10.7	4.7	100

NC = **Not collected**
NOTES: Data is for 41 States responding to the survey.
Stations not included are Alabama, Alaska, Connecticut, Delaware, District of Columbia, Idaho, Nevada, New Mexico, North Dakota, Pacific Territories, Virgin Islands, Vermont, Wyoming.
The 1984 survey was different from the other three and not completely compatible.

SOURCE: National Association of State Universities and Land Grant Colleges, Division of Agriculture, Committee on Biotechnology, "Emerging Biotechnologies in Agriculture: Issues and Policies, " Progress reprots I thru VIII, November, 1982-1989.

Table 16-11—Biotechnology Research Funds for 12 Largest State Agricultural Experiment Stations, 1966°

	USDA	USDA competitive	Other Federal	State	Private	Other	Total
Total funding (million $)	**9.96**	**6.48**	**18.58**	**34.70**	**9.47**	**4.50**	**83.69**
Distribution of biotech funds by source (percent)	**11.9**	**7.7**	**22.2**	**41.5**	11.3	**5.4**	100.0
Share of total biotech funds (percent)	**54.5**	**64.9**	**67.4**	**62.9**	**67.7**	**72.1**	**63.8**

[a]12 SAES include California, Florida, Iowa, Indiana, Illinois, Michigan, Minnesota, Nebraska, New York, North Carolina, Texas, Wisconsin.
Data for total funding does not include the stations of Alabama, Alaska, Connecticut, Delaware, District of Columbia, Idaho, Nevada, New Mexico, North Dakota, Pacific Territories, Virgin Islands, Vermont, Wyoming.

SOURCE: National Association of State Universities and Land Grant Colleges, Division of Agriculture, Committee on Biotechnology, "Emerging Biotechnologies in Agriculture: Issues and Policies, " Progress reports I thru VIII, November, 1982-1989.

conducts an experiment to test it. Research in computer systems does not easily lend itself to this approach and traditional agricultural journals are reluctant to publish articles on computer application. Research in advanced computer applications require a multidisciplinary effort by domain experts and computer scientists and cannot, in general, be performed by a single scientist. Multidisciplinary development efforts currently cannot be adequately recognized solely through publications. In fact, the end result of most computer-related research projects

is a marketable product not a manuscript. And, advanced computer applications are perishable. Once a system is developed, it will generally require regular maintenance to ensure that the information and knowledge are current. Consequently, there exists a perception, especially among conservative faculty, that advanced computer technology research does not represent an appropriate topic for academic professionals. This technology will challenge traditional institutional arrangements.

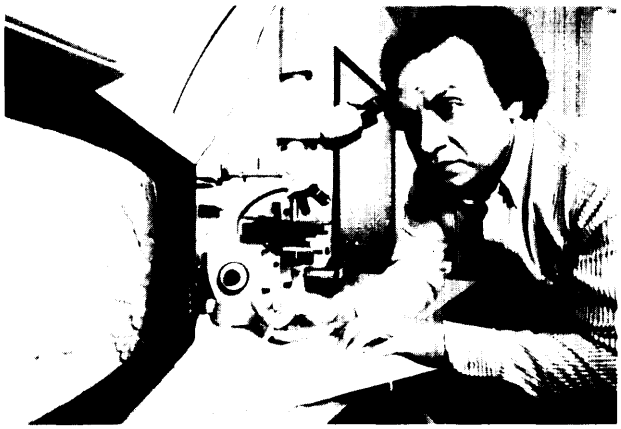

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Biotechnology research requires a thorough knowledge of agriculturally related biological and natural sciences. Only 16 percent of agricultural scientists working in academia received PhDs in basic disciplines underlying this new technology.

Photo credit: U.S. Department of Agriculture, Agricultural Research Service

Development of advanced computer technology relevant to agriculture is impeded by funding and a professional reward system in State Agricultural Experiment Stations that does not support the development of computer systems.

The Legal Environment

The legal environment in which the agricultural system operates is changing. As discussed in chapter 15, Congress has for the past 60 years expressly permitted intellectual property protection of new plants. Since 1980, the U.S. Patent and Trademarks Office has interpreted patent laws to cover not only plants but also microorganisms and animals as patentable subjects (14). The Patent and Trademark Amendments (Public Law 96-517, 1980 and amended in 1984) gave universities, other nonprofit organizations, and small businesses the option, with few exceptions, to retain the title rights to any federally funded inventions that they developed. The same rights were extended to large businesses by executive order (14). Legislation has also been enacted to facilitate technology transfer between Federal laboratories and industry. The Stevenson-Wydler Technology Innovation Act of 1980 (Public Law 96-480) provides Federal laboratories with a mandate to undertake technology transfer activities, while the Technology Transfer Act of 1986 (Public Law 99-502) created an organizational structure to meet this mandate.

The changing legal environment in which the agricultural system operates is changing the system itself. Universities are creating new structures to take advantage of these "legislated" opportunities. Until recently, only a few institutions (i. e., the Massachusetts Institute of Technology and Stanford University) aggressively marketed the research of their faculty, primarily by licensing their technology to the private sector. Now, however, other universities are establishing venture capital pools, technology development companies, and research companies with the goal of transferring technology and making money.

Universities have usually patented their inventions, so patenting per se does not represent a significant change. And not surprisingly, the universities receiving the most patents are generally larger, research intensive institutions (table 16-12), Among those universities receiving the most patents in 1989, six are land-grant universities.[2] As discussed previously, the sale of products by the SAES

[2]The six land-grant universities are Massachusetts Institute of Technology, which does not have a SAES, and the University of California, the University of Florida, Iowa State University, the University of Minnesota, and the University of Wisconsin, which do have SAES. Patent figures are for the whole university, and not exclusively the SAES.

The patent awarded to Stanley Cohen and Herbert Boyer in 1980. This patent has since become Stanford University's top earning patent ($1.7 million annually).

United States Patent [191

Cohen et al.

[11] **4,237,224**

[45] **Dec. 2, 1980**

[54] **PROCESS FOR PRODUCING BIOLOGICALLY FUNCTIONAL MOLECULAR CHIMERAS**

[75] **Inventors:** Stanley N. Cohen, Portola Valley; **Herbert W. Boyer, Mill** Valley, **both of Calif.**

[73] Assignee: **Board of Trustees of the Leland Stanford** Jr. University, Stanford, **Calif.**

[21] Appl. No.: **1,021**

[22] Filed: **Jan. 4, 1979**

Related US Application Data

[63] Continuation-in-part of Ser. No. 959,288, Nov. 9, 1978, which is a continuation-in-part of ser. No. 687,430, May 17, 1976, abandoned, which is a continuation-in-part of ser. No. 520,691, Nov. 4, 1974.

[51] Int. Cl. C12P 21/00

[52] U.S. Cl. ..... 435/68; 435/172; 435/231; 435/183; 435/317; 435/849; 435/820; 435/91; 435/207; 260/1 12.5 S; 260/27R; 435/212

[58] Field of Search ..... 195/1, 28 N, 28 R, 112, 195/78, 79; 435/68, 172, 231, 183

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Primary ***Examiner—*** Alvin E. Tanenholtz

Attorney, Agent, or Firm-Bertram 1. Rowland

[57] ABSTRACT

Method and compositions are provided for replication and expression of exogenous genes in microorganisms. Plasmids or virus DNA are cleaved to provide linear DNA having ligatable termini to which is inserted a gene having complementary **termini, to provide** a biologically functional replicon with a desired phenotypical property. The replicon is inserted into a microorganism cell by transformation. Isolation of the transformants provides cells for replication and expression of the DNA molecules present in the modified plasmid. The method provides **a** convenient and efficient way to introduce genetic capability into microorganisms for the production of nucleic acids and proteins, such as medically or commercially useful enzymes, which may have direct usefulness, or may find expression in the production of drugs, such as hormones, antibiotics, or the like, fixation of nitrogen, fermentation, utilization of specific feedstocks, or the like.

14 Claims, No Drawings

SOURCE: Office of Technology Liensing, Stanford Unversity

Table 16-12—Universities Receiving the Most Patents, 1989

Massachusetts Institute of Technology[a]	102
University of California[a]	81
California institute of Technology	59
University of Texas	57
Stanford University	43
University of Florida[a]	42
University of Minnesota[a]	41
Iowa State University[a]	28
University of Wisconsin[a]	28
Johns Hopkins University	27

*Land-grant universities.
SOURCE: Association of University Technology Managers, 1991

Table 16-13—USDA Agricultural Research Service Technology Transfer Activities, 1987-1990

	1987	1988	1989	1990
Number of patents awarded	34	28	47	42
Royalties from licenses (in thousand dollars)	85	97	418	567
Number of active CRADAS	9	48	86	104
Value of active CRADAS (in million dollars)	1.6	8.7	15.6	18.9

SOURCE: Data provided by staff of USDA Agricultural Research Service, Office of Cooperative Interactions, 1991.

increased from $58.5 million in 1982 to $83.4 million in 1989.

What is different is that universities now have title to the patent rights, even if the research was federally funded. Thus, universities now own pieces of or are otherwise involved with new ventures that invest in and commercialize the new technologies they developed. Universities, in some cases, seethe new ventures as a means of establishing closer cooperation with private companies, ultimately with the goal of inducing the private sector to contribute research funding to the university, of facilitating the transfer of the technology, and of helping faculty to see the relevance of their work to real world problems. In addition, the researchers who create the new technology are now often given a share of the returns. Some examples help to illustrate the new arrangements.

Iowa State University has a research budget of over $110 million annually and conducts over 2,500 research projects. The goal of the university is to create new businesses and generate new revenue and new jobs. Emphasis is being given to biotechnology. The university keeps track of all research and helps obtain patents when needed. It has even built a pilot manufacturing plant to test a new innovation and eventually hopes to entice a private company to provide capital for an expanded operation (1 1).

The Southwestern Medical Center at the University of Texas has established a for-profit company with $12.5 million in equity from a private venture capital firm and individual investors. The center retains a stake in the company and expects to share any profits (11). Other approaches include establishing joint projects with other institutions. The University of Chicago and the Argonne National Laboratory have created a not-for-profit corporation that will develop and market inventions produced by scientists at the two institutions. The Universities of Texas and Chicago are not land-grant universities, but the types of institutions described could serve as a model for the development of similar institutions at the land-grant schools.

Federal research laboratories also are responding to the new incentives, and to congressional wishes that they do a better job of transferring their research results to the private sector. The USDA Agricultural Research Service (ARS) has entered into 104 Cooperative Research and Development Agreements (CRADAS) with private industry valued at nearly $19 million. Additionally, ARS patents its research findings and in 1990, received $567,000 from royalties on licenses issued (table 16-13).

ISSUES RAISED BY THE NEW ENVIRONMENT

The changing environment in which the agricultural research system operates raises three main issues for the system:

1. What is the appropriate allocation of existing resources'?
2. Who decides what the appropriate allocation is?
3. How is the system to be structured to effectively achieve the desired allocation'?

As indicated by the high rates of social return to agricultural research investments, the system as a whole has not been funded at optimum levels, and there is a general need for more research funding. However, increased research funding is not sufficient to achieve desired results. Funds also need to be reallocated from current projects to research that reflects new needs. The appropriate allocation of resources will depend primarily on what society wants the system to accomplish. Resources cannot be allocated appropriately unless priorities are determined and goals established.

Land-grant universities differ from other universities in that they have a legislated mission to address research to the problems of society. Some argue that the land-grant system has, at least to some extent, already abandoned its mission, as researchers increasingly work for the laurels of their disciplinary peers rather than society's benefit. Others argue that the system defines society's problems too narrowly and places too much emphasis on increasing agricultural productivity and too little on nutrition, environmental, and rural problems. Some also argue that too much attention is given to production agriculture and not enough on postharvest technologies, value-added products, consumer preferences, and agribusiness problems.

There are no easy answers as to what types of research should be conducted with public funds. What is clear, however, is that as the traditional clientele (i.e., farmers) continues to shrink, greater demands will be placed on the system to address the needs of other groups. Difficult choices must be made concerning the mix and prioritization of research.

Historically, decisions on how research funds were allocated were made at the local institutional level. This approach was because most funds were awarded to institutions as block grant formula funds. The institution, with input from local clientele, determined how the funds should be administered. However, competitive grants, from USDA and other Federal agencies are an increasing component of total funding, and these grants are awarded to individual researchers or projects. Project proposals reflect the individual researchers personal interests and views of social needs. Decisions concerning which proposals are awarded grants are made by peer review at the national level.

The shift toward greater reliance on project funding (competitive grants) rather than institutional funding (formula funds) is an attempt to induce greater responsiveness of the State system to national priorities. Additionally, the wider competition increases the pressure to perform and be more productive. However, these goals must be balanced against the potential losses that come from not being part of a larger mission and attentive to local needs and from the potential lack of continuity that might come from a competitive grants program (11). Additionally, it is argued that competitive grants may shift the research focus from solving society's problems to short-term projects, the results of which are more readily publishable in peer reviewed journals.

An increase in research funds from the private sector has raised a great many concerns. The actual extent of private sector-public university collaboration is unknown, but university administrators suspect that it is not yet extensive. Industry funding of research at the SAES comprises about 6.5 percent of total funding, and that share has not dramatically increased over the past decade. Industry support of biotechnology research is higher than for agricultural research in general, but even in this area, funding from industry represents about 11 percent of total funding.

Industry support for university research is not expected to continue growing rapidly. Private firms are decreasing their own research budgets and may not have the money to spend on university research. The biotechnology industry appears to be undergoing the long expected shakeout, with many smaller, dedicated biotechnology firms consolidating, retrenching, or going out of business. The large firms that likely will remain major players in the area of biotechnology research have now developed their own in-house research capacity. Industry financing of university research will be directed toward specific fields that industry feels will be most beneficial to them, and may be leveling off.

The changes in the legal environment combined with constrained research budgets provide many incentives for universities to increase funding through product sales. This potential privatization of public sector research raises many issues. Product sales currently represent only 5.5 percent of total research funding, but whereas growth potential in other sources of funding seem limited, there is a possibility of high growth in revenue from the sale of university inventions.

Incentives to privatize the benefits of university innovations for the benefit of the university rather than society could conflict with the mandated mission of the university. Using public resources to reap private gains raises many ethical questions. The situation of allowing individual researchers to share in the profits of their work, even if it was publicly funded, and of encouraging universities to produce consumer products opens the door to potential abuses.

Certainly there is potential for conflicts of interest if universities and individual researchers are allowed to capture the returns of their innovations. To some extent, this same issue is raised when researchers use public funds to generate new knowledge that can be sold to the private sector in the form of consulting fees. But there is a distinction between providing expertise to potentially multiple clients and having a vested interest in the development of one or several products by companies. The credibility of a university may suffer if it is viewed as

being too cozy with industry. An interesting dilemma may arise for a university if its researchers identify significant hazards with a product or technology that generates profits for the university, or for a company with which the university collaborates. If public universities prioritize their own private good above the public welfare, the public may not maintain its support for the university. On the other hand, given the underinvestment in agricultural research as a whole, the additional revenue from product sales could provide great benefits for the university and society. Whether or not the funds are used for desirable purposes will depend on how well university administrators provide leadership to maintain a sense of priority for the overall research and teaching mission, and whether they have the administrative skills to allocate resources to the proper ends.

Channeling more resources to innovative activities from which private return can be reaped may alter the focus of research. There could be a shift in the research mix from research that is a public good to that which will be attractive to industry. University research potentially could shift from long-term research to more short-term projects that are likely to have quick payoffs. There is also concern that changes in intellectual property rights will cause universities to change the focus of their research. Results of a preliminary analysis (5) suggest that intellectual property rights do influence the amount of resources devoted to specific commodity research in universities (i. e., universities do allocate more resources to research on commodities where they can get Plant Variety Protection Act certificates and capture some of the returns to their research). Results suggest, however, that universities do not direct more public sector funding to commodity research supported by industry funding. The agricultural research system often is criticized for focusing too much attention on basic research and little on development and adaptive research to solve social problems; a shift toward practical technologies and products may be perceived by some as a positive outcome.

One of the underlying principals of scientific research is the free exchange of research results. Concern has arisen that if research begins to generate income, it could become more proprietary. The free exchange of germ plasm between individual researchers and countries may be inhibited as germplasm owners seek to profit from that germplasm. Moreover, research results may be exchanged less freely, or exchanged only after the researcher, university, or industry supporting the research attempts to patent the results or seeks additional private-sector funding. The growing tendency of researchers to announce their results via press release rather than in peer-reviewed journals may also, at least to some extent, be an attempt to attract the attention of private industry and to enhance the opportunity of obtaining private funding for further work. One unfortunate fallout of these activities is to confuse a public that has little understanding of scientific issues, and thus to diminish the credibility of scientific research.

Concern also has been expressed that the potential for financial rewards will lead to the exploitation of graduate students by faculty advisers. If, for example, students are directed toward research designed to benefit a particular company or are not allowed freely to publish their research results, their future employment opportunities could suffer.

Finally, it is likely that only some universities will benefit from collaborations with the private sector. The same universities that receive the bulk of the public-sector funding also attract the most private-sector funding, patent the most innovations, and receive the largest revenue from the sale of products. As the costs of maintaining university programs continue to rise, then only schools that can attract private revenue may be able to continue to maintain a full research, teaching, and extension function. Smaller universities most likely will need to reorganize and cooperate on a regional basis to maintain research programs. Neither Federal formula funds nor competitive grants nor State funding mechanisms are designed to accommodate cooperative institutional arrangements.

RESEARCH TO EVALUATE IMPACTS OF THE NEW ENVIRONMENT

The above discussion has been based on possibilities and speculation. There is little information available on what changes actually are occurring at the SAES as a result of the changing research environment. No comprehensive data exist on the present extent of collaboration between the public and private sector; on the nature of existing arrangements; or on the amount and uses of revenue generated from such arrangements and how that revenue is being used. Data also do not exist on how additional revenue is being used to support socially desirable but underfunded research, or to support teaching activities. It is unknown to what extent existing university-private sector arrangements create additional economic activities. Any discussion of these issues is based on speculation and anecdotes—u more rigorous analysis is needed.

Likewise, little is known about how increasing reliance on competitive grants is impacting agricultural research. It is widely presumed that the research supported via a competitive grant mechanism is of higher quality than that funded by formula funds, and that greater reliance on competitive grants increases productivity. However, it is also possible that competitive grants distort the research mix favoring disciplinary research over problem-solving research.

Little research has been conducted to determine the productivity of the different funding mechanisms. However, recent research completed by OTA and the University of Minnesota suggest that the most appropriate policy is a mixture of formula and competitive grants, with different funding mechanisms potentially more appropriate for different functions and goals of land-grant universities (19).

The data set used to analyze the productivity of different funding mechanisms is a subset of agricultural research at SAES. This subset is for fiscal year 1986 research projects that are receiving at least some funding from USDA and at least some portion of the research project involves using the tools of biotechnology. The biotechnology data set was chosen because trends that seem to be occurring within land-grant universities appear to be magnified in the area of biotechnology research. Therefore, whatever is occurring in that subset of research may be indicative of future changes in other fields of agricultural research. The data set includes research funded by Hatch grants, USDA Competitive grants, and Other grants which include State grants, Evans-Allen grants, Animal Health grants, and McIntyre-Stennis grants (i.e., formula funds somewhat analogous to Hatch funds). Data was obtained from the Cooperative Research Information System (CRIS) and includes publications as reported by the principal investigators

Output is measured by publications including peer reviewed journal articles (published articles, abstracts, articles in press, and articles submitted), experiment station bulletins, and graduate student degrees. These types of publications were chosen because they can be used as measurable proxies to represent the research, teaching, and extension missions of the land-grant system. Quality of published peer reviewed journal articles was measured by the number of citations the article received. Citations are not a perfect measure of quality, but are widely used.[4]

Findings from this research suggest that different types of publications are more likely to be funded by different sources. (See table 16- 14.) The actual number of journal articles per grant did not differ significantly by funding source, however, articles published from research funded by competitive grants were cited much more frequently than research articles funded by other mechanisms. Also, competitive grants provide funding for fewer years and generally are for lower levels of funding than Hatch grants, suggesting that for cutting-edge research, competitive grants are more productive and of higher quality. However, Hatch funding supports more research students, and generally produces a higher number of experiment stations bulletins, which are geared to be more useful to farmers and others in the industry and may be more representative of adaptive research than are many journal articles.

The conclusion suggested by these results is that different funding mechanisms may be more appropriate for different goals of the university system. If the goal is to increase cutting-edge research, competitive grants might best be emphasized. If the primary goal is to enhance research applicable to problem solving (more development and adaptive research and technology transfer) or to train future researchers, the more stable and locally controlled Hatch funds may be the more appropriate mechanism. The appropriate allocation of the two types of grants depends on the priority given to the multiple missions of the experiment stations. However, developing mission priorities is not a simple task. Research

[3] The total number of grants have been normalized to account for the fact that while all projects were being funded in FY 1986, some projects received their initial funding in that year while others had been funded for several years. For example, for Hatch grants and other grants, over 50 percent of the projects received initial funding prior to 1985. For competitive grants, only 25 percent of the grants had received initial funding prior to 1985. **Previous research** has shown that it generally takes about four years of funding before significant levels of output can be expected (8). However given the recent nature of biotechnology research, significant levels of funding did **not exist prior to 1982. This is why 1986 and 1987 publications were** chosen as the data set. However, for many of the projects funding had not occurred for four years. It is unreasonable to expect a research project which has been funded for one year to produce as many articles as one which has been funded for several years and the grants were normalized to account for this difference. (The actual normalization equation was as follows: (grants in 1982) + 4/5(grants in 1983) + 3/5(grants in 1984) + 2/5(grants in 1985) + 1/5(grants in 1986).)

[4] Citations indicate that other researchers have read and used the work. However, not all citations may be positive. Additionally, review articles are likely to be sighted more often than other types of articles. It is also possible that an article is of high quality, but is in a field that not many other researchers are working, and therefore the number of citations may not be a good measure of the quality of the article. It may also be the case that an article is cited only by the author of the article (self cites). One might argue that the research was useful in furthering the work of the author, but that may not represent input into other researcher's work. Citations were corrected by subtracting self-citations.

Table 16-14—Mean Values of Selected SAES Output by Grant Type

	Hatch	Competitive	Other
Citations per article[a]	1.70	3.98'	1.82
Articles per grant	2.47	2.14	2.24
Weighted articles per grant[b]	4.83	8.33[f]	4.74
Journal publications per grant[c]	4.70	4.52	3.68
Weighted publications per grant[d]	7.07	10.62[g]	6.58
Degrees per grant	**0.45'**	**0.18**	**0.25**
Bulletins per grant	0.35	0.09'	0.28

[a] Articles are articles published in peer reviewed journals
[b] Weighted articles are published articles weighted by citations
[c] Journal pubs are published articles, articles submitted, articles in press, and abstracts in peer reviewed journals.
[d] Weighted pubs are articles submitted, articles in press, and abstracts in peer reviewed journals, and published articles weighted by citations
[e] Significantly different from other two groups at 950/. confidence level
[f] Significantly different from other two groups at 94% confidence level
[g] Significantly different from other two groups at 920/. confidence level.

SOURCE: Mane Walsh, "Factors Affecting the Cost and Productivity of Biotechnology Research at the State Agricultural Experiment Stations", PhD thesis, University of Minnesota, in progress.

is needed to analyze what sort of institutional structure can best involve all relevant clientele in priority and goal setting for SAES.

POLICY OPTIONS

ISSUE: The new partnership between the public- and private-sectors potentially can revitalize agricultural research, but could also bias the overall research endeavor and destroy the credibility of universities. Research and close monitoring will be needed to understand the changes occurring within the land-grant system and to ensure that they are not undermining the system as a whole.

Option: Congress could require the U.S. Department of Agriculture to monitor the increased private-sector funding of agricultural research and to prepare an annual report to Congress containing the data.

Currently, little is known about the extent of private-sector funding at land-grant universities and the nature of the relationship between the universities and the private sector. Congress could provide oversight of this situation by periodically conducting oversight hearings. Furthermore, Congress could request that USDA collect data from the land-grant universities on the extent of public-private collaboration, prepare an annual report to Congress containing the data, and provide guidelines on the appropriateness of various public- private-sector research collaborations.

Option: Congress could direct USDA to require land-grant universities to establish an explicit policy with regard to research sponsored by the private-sector and report that policy to Congress.

The USDA would require each university using private-sector research funds for agriculture to establish a policy as to how those funds are used. Establishing an advisory board that includes members of the public in setting spending priorities for the funding of research from the private sector might be an effective mechanism. This would help to increase the confidence of the public that the university is using these funds to solve problems that confront society.

Option: Public-sector support of social science research could be increased.

Understanding the complex institutional changes occurring in the public agricultural research system will require increased social science research. Currently, social science research is underfunded by the public sector, and it is highly unlikely that the private sector will support this kind of research. Lack of social science research may constrain the ability of the land-grant system effectively to understand and the control the changes that are occurring and to address the problems of society as its mission dictates.

ISSUE: **High rates of return to public-sector investments have been reported by numerous studies. This a clear indication that public-sector research funding is below socially optimum rates.**

Option: Congress could increase public-sector support of agricultural research.

Increasing public-sector support of agricultural research might help to lessen the pressure on land-grant universities to try and obtain funds from the private sector. Given the high rate of return on public-sector funding of agricultural research, increased funding is a good investment for the future.

Option: Congress could maintain or decrease public-sector funding for agricultural research.

Federal funding for agricultural research has been relatively flat for the last 30 years. As a consequence States have picked up the increased costs of conducting agricultural research. It is difficult for States any longer to take on an ever increasing share of public supported research. If the Federal Government continues to shrink from its partnership with the States in the funding of

research, land-grant universities have no choice but to look for alternative sources of funding. Private-sector funding from specific industries or individual firms or product sales from technologies developed by the university are the most likely sources of additional research funds. The impact of this shift in support is unknown and needs further analysis.

ISSUE: Land-grant universities have been and are now rapidly developing into "have and have not" universities. In this situation it is difficult for the "have not" universities to individually fulfill their historic responsibilities.

Option: Congress could increase Federal funding for multiregional projects as opposed to institutional or individual funding.

There is nothing magic about State Boundaries, yet they have defined agricultural research problems since the inception of the research system. Most cultural problems and solutions, however, are more appropriately defined within and across geographic regions. Universities would be better able to collaborate on common agricultural problems or to specialize in certain areas for the region where they have a critical mass of expertise. The major disadvantage is State leaders accepting this concept after so many years of expecting their university to provide the research, teaching, and extension to solve their problems and provide education.

Option: Congress may wish to allow the States to find their own solutions to this growing problem.

The States would have the major responsibility for finding a solution. This could be in the form of increased funding to the university to provide at least minimal services in all traditional activities eliminating some activities and reallocating those funds to high priority activities or working with other States to jointly determine activities suitable for cooperation. However, if the decision is to work with other States the Federal Government could be an obstacle by placing a constraint on the proportion of Federal funds that can be used for regional projects.

ISSUE: Recent research indicates that public sector funding mechanisms should be goal oriented.

Option: Congress could appropriate funds for agricultural research through funding mechanisms based on well-defined goals.

The land-grant system provides teaching, extension, and research functions. Preliminary research indicates that Hatch formula are more conducive to teaching and extension activities and competitive grants more conducive to basic research. By appropriating funds via goals to be achieved, Congress could improve the effective use of public funds.

Option: Congress could maintain the current emphasis of increased funds for competitive grants and level or decreased funding of formula and intramural funds.

Implicitly, this would indicate that Congress places. greater emphasis on basic research than on adaptive research, extension, and teaching activities. Evidence does not exist that the lack of basic research is the primary constraint to the ability of land-grant universities to fulfill their historic mission of addressing research aimed at serving societal problems.

Option: Congress could extend competitive grants to extension and teaching curriculum development.

A strong case can be made for formula funding of agricultural research. However, if politically the only acceptable form of increased funds is competitive grants, then expanding these grants to also include adaptive research, extension, and teaching could be considered. Balanced funding of basic research, adaptive research, teaching, and extension would significantly strengthen the land-grant universities and help them meet their multiple missions more effectively.

Option: Congress could award some competitive grants to basic research that ties successfully into adaptive research.

This would be a clear signal that Congress considers the original mission of land-grant universities to be appropriate today. Currently, most grants for basic research are not tied directly to adaptive research. Thus, it is difficult to differentiate between funding provided by the National Science Foundation (the major funding agency for basic research) and the U.S. Department Agriculture (a major funding agency for mission-oriented adaptive research).

ISSUE: The public is increasingly losing confidence in land-grant universities. Credibility needs to be restored. Development of a more mission-oriented system with increased public input would help to restore confidence in the system.

The OTA report *Agricultural Research and Technology Transfer Policies for the 1990s (15)* addresses this issue in some detail and provides specific options that suggest changes in the system to make it more mission oriented. Those options are incorporated here by reference. Some of the options were incorporated into the 1990 Food, Agriculture, Conservation, and Trade Act of 1990 (1990 Farm Bill).

ISSUE: Few professional benefits exist for conducting adaptive and multidisciplinary research or to effectively communicate the purpose of university research to the public. Continuing focus on basic, disciplinary research that is communicated only to peers enhances the public's perception that research is irrelevant and undermines the public willingness to support such research.

Option: Land-grant universities could develop professional rewards for researchers conducting adaptive or multidisciplinary research.

A change at land-grant universities to reward researchers for adaptive or multidisciplinary research and those that communicate well the purpose and results of research to the public will be difficult to achieve. In many universities, determination of reward criteria goes beyond research administrators to include faculty committees, which in many cases have the last word on the university's reward criteria. And, faculty who comprise these committees are, for the most part, basic scientists. Until such time that these committees' composition is changed or their power diminished, it will be difficult for any change to occur. The only leverage available is through those that control research funding. Thus, more strings could be attached to Federal grants that provide incentives for adaptive research, multidisciplinary research, and communication of results. This is especially crucial for research in advanced computer technologies. This promising area will continue to languish unless changes are made to reward researchers in these other areas in addition to basic research.

Option: Land-grant universities could maintain the status quo by continuing to provide the highest professional awards for basic research.

In the short run this option will be the path of least resistance. But in many ways, it will be costly in the long run. Following this course leads to the fundamental question of the difference between a land-grant university and any other university. Why should the public uniquely support universities that provide a product no different from other universities? If there is no difference then it is difficult to provide a rationale for the special public funding provided to land-grant universities. Indeed, such funding is to be used by the university to provide a service to society that is unique.

ISSUE: **Advances in the application of advanced computer technologies require establishing this field of research as a priority. Currently, research in this area relies on ad hoc funding from numerous scientific disciplines and weak ties to basic computer science and the private sector. Research for advanced computer systems requires a nontraditional approach and multidisciplinary teams that include computer scientists, traditional production-oriented scientists, business, marketing, and policy specialists, and system designers.**

Option: Congress could establish nationally recognized centers of excellence for advanced computer technology research.

The Federal Government, States, and the private sector could jointly establish centers of excellence at various land-grant universities. These centers would involve the various university departments that comprise SAES, computer science, the business school, etc. The center concept has worked well in other major technological areas such as biotechnology. It provides a focus for research with continuity. A drawback is the lack of incentive for faculty, especially young, untenured faculty, to participate in multidisciplinary research.

Option: Congress could establish this area as a priority with increased funding to land-grant universities.

Funding would be available through various types of grants much like other scientific disciplines. To enhance the multidisciplinary effort, grant applications could be required to contain a strong adaptive component conducted by a multidisciplinary team. However, this is still an ad hoc approach. A project investigator (PI) must convince scientists in other disciplines that it is in their best interest to be a part of the project. Even if the PI is successful there is no guarantee of any continuity of interest. Once the project is completed, team members go back to their respective disciplines. Also, as mentioned above, it would be difficult to entice young, untenured faculty to participate. At best this approach is only a step above the current situation.

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Appendixes

Appendix A
Glossary of Acronyms

ABRAC	—**Agricultural** Biotechnology **Research Advisory Committee** (USDA-OAB).
AEAES	—Agricultural Financial Analysis Expert System. A computer system combining a spreadsheet, program calculator, and expert systems to assist farmers with financial planning and analysis; developed by Texas A&M University
AID	—Agency for International Development
AMS	—Agricultural Marketing Service (USDA)
APHIS	—Animal and Plant Health Inspection Service (USDA)
ARS	—Agricultural Research Service (USDA)
BATF	—Bureau of Alcohol, Tobacco and Firearms
BBEP	—Biotechnology, Biologics and Environmental Protection Division (USDA-APHIS)
BITNET	—A national network of interlined mainframe computers
BRS	—Biotechnology Research Subcommittee (FCCSET); successor to BSCC
BSAC	—Biotechnology Science Advisory Committee (EPA)
BSCC	—Biotechnology Science Coordinating Committee (interagency); succeeded by BRS
CBA	-Committee on Biotechnology in Agriculture (USDA-OAB)
CBI	-Confidential Business Information. Protected information, the disclosure of which could damage a firm's competitiveness
CES	-Cooperative Extension Service (USDA)
CFSAN	-Center for Food Safety and Applied Nutrition (FDA)
COC	-Council on Competitiveness (executive branch)
COMAX	-Cotton Management Expert System. An expert system developed by the USDA that **uses a simulation model of cotton production to project when to irrigate and fertilize to optimize agronomic goals**
CROPS	**-Crop Rotation Planning System. A computer program developed at Virginia Tech to assist with farm-level or field-level planning**
CVM	**-Center for Veterinary Medicine (FDA)**
DHI	**—Dairy Herd Improvement. A national data recording system developed for the dairy industry; provides centralized databases** from which expert systems can be built
EA	**—Environmental Assessment**
EBC	**—Environmental Biosafety Committee (EPA)**
EC	**—European Community**
EPA	**—Environmental Protection Agency**
ERS	**—Economic Research Service (USDA)**
ESA	**—Ecological Society of America**
EUP	**—Experimental Use Permit**
FCCSET	**—Federal Coordinating Council on Science, Engineering and Technology**
FDA	**—Food and Drug Asministration**
FD&C (FDCA)	**—Food, Drug and Cosmetic Act**
FIFRA	**—Federal Insecticide, Fungicide, and Rodenticide Act**
FMIA	**—Federal Meat Inspection Act**
FOIA	**—Freedom of Information Act**
FONSI	**—Finding of No Significant Impact (from an Environmental Assessment)**
FS	**—Forest Service**
FSIS	**—Food Safety and Inspection Service (USDA)**
GAO	**-General Accounting Office**
GATT	**-General Agreement on Tariffs and Trade**
GRAS	**-Generally Regarded as Safe. Status granted to substances that are acceptable as human foods or as ingredients in human food, as determined by qualified experts based on a safe history of use in food prior to 1958; or based on published scientific information**
IBC	**—Institutional Biosafety Committee**
LISP	**—List Processing. A high-level computer programming language used in artificial intelligence applications**
NAS	**—National Academy of Science**
NEPA	**—National Environmental Policy Act**
NBIAP	**—National Biological Impact Assessment Program (USDA-CSRS)**
NIH	**—National Institutes of Health**
NMFS	**—National Marine Fisheries Service**
NOAA	**—National Oceanic and Atmospheric Administration**
NOEL	**—No Observable Effect level (refers to dosages of pesticide fed to test animals)**
NRC	**—National Research Council**

NSF —*National* Science Foundation
OAB -Office of Agricultural Biotechnology (USDA)
OECD - .“on for Economic Cooperation and Development
OMB -Office of Management and Budget
OPP -Office of Pesticide Programs (EPA)
ORA -Office of Regulatory Affairs (FDA)
OSTP -Office of Science and Technology Policy
OTA -Office of Technology Assessment
OTS -Office of Toxic Substances (EPA)
PMN —Premanufacture Notice. Requested by EPA for Commercial R&D involving field-test releases of genetically engineered microorganisms; compliance is voluntary
PPA —Plant Patent Act
PPIA —Poultry Products Inspection Act
PTO —Patent and Trademark Office
PVPA —Plant Variety Protection Act
RAC —Recombinant DNA Advisory Committee (NIH)
SAES -State Agricultural Experiment Stations (USDA)
TSCA —Toxic Substances Control Act
UCC —Universal Copyright Convention
UPOV —International Union for the Protetion of New Varieties of Plants
USDA —United States Department of Agriculture
WHO —World Health Organization

Appendix B
Glossary of Terms

Acetolactate Synthase (ALS): Enzyme essential for plant growth; the target site in pest plants for many new herbicides known as ALS *inhibitors.*

Algorithm: An unambiguous step-by-step procedure for solving a problem or modeling a process; commonly used as fundamental parts of computer programs.

Allelochemicals: Herbicides produced by plants.

ALS inhibitor: Herbicides that attack target plants by binding to and inactivating the ALS enzyme essential for plant growth.

Amino acid: Any of a group of molecules linked together in various combinations to form proteins. Specific sequences of amino acids makeup all known proteins, with each unique sequence coded for by DNA.

Antibody: Protein produced by specific white blood cells (i.e., B lymphocytes) in response to the presence of foreign antigens in the body.

Antigen: Any substance that elicits a defensive (immune) response.

Antisense technology: A technique for eliminating or reducing the expression of a gene in an organism, thus enabling scientists to study the organism's physiology and development.

Arthropods: A phyllum of invertebrate animals that includes spiders, mites, and ticks; insects; centipedes and millipedes; and crustaceans (shrimp, barnacles, crabs).

Assay: Experiment, test or analysis.

Augmentation approach (to biological pest control): Increasing an existing population of indigenous pest enemies by periodically releasing small numbers of these natural enemies, or by releasing large numbers of these enemies at one time.

Bacillus thuringiensis (Bt): A spore-forming bacterium that produces insecticidal proteins. Different strains of Bt produce proteins toxic to different insects. Through genetic engineering, the insecticidal genes from different Bt strains have been incorporated into other organisms, including plants, which then produce the corresponding Bt toxin.

Bacteria: A diverse and ubiquitous group of one-celled organisms that lack a distinct nuclear membrane.

Bacteriophage: A virus whose host is a bacterium.

Beltsville pig: A pig, developed through research at the USDA in Beltsville, MD, into which extra growth hormone genes were inserted. The Beltsville pig provides a clear example of biotechnology that compromised an animal's well-being-the pig grew fast but became lame and lethargic, developed degenerative joint disease and a variety of other disorders, and clearly was under stress.

Biological control (of pests): Use of living natural enemies to reduce pest populations.

Biopesticides: Organisms or products containing organisms that are pesticidal in nature; used for the *biological control* of pests.

Biotechnology: Techniques, including recombinant DNA techniques, that use living organisms or substances from those organisms to make or modify a product, to alter the characteristics of plants or animals, or to develop microorganisms for specific uses.

Bolistic method (of gene transfer): A vectorless method of transferring genes using a particle gun to shoot high-velocity, DNA-coated microprojectiles into a plant cell.

Bovine somatotropin (bST): See *Somatotropin.*

Broad leaf herbicides: Herbicides that attack broad leaf plants or DICOTYLEDONS; will not harm grass plants *(monocotyledons)* such as corn.

Broad spectrum herbicide: Herbicide that can kill broad-leaf weeds as well as grasses.

Cell culture: The growth and maintenance of cells derived from multicellular organisms under controlled laboratory conditions. A sample of cells propagated in this way.

Cellular techniques (for genetic modification of plants): Use of tissue cell cultures to genetically modify plants, e.g., hybridization of two sexually incompatible plants via cell fusion.

Chromosome: A thread-like structure (of DNA molecules) carrying the genes that convey hereditary characteristics; in mammals chromosomes are contained in cell nuclei.

Classical approach (to biological control of pests): Generally involves searching the area of a pest's origin for its natural enemies and introducing these enemies into the environment in which the pest is to be controlled.

Classical techniques (for genetic modification of plants): Generally refers to the use of traditional plant breeding to develop plants with certain desired characteristics, such as insect or disease resistance, improved harvestability, cold tolerance, etc.

Clone: A group of genetically identical cells or organisms produced asexually from a common ancestor.

Community ecology: The study of the interactions of populations of different species in a habitat.

Computer network: A system of interconnected electronic channels linking computers over a wide area; allow rapid dispersal and sharing of information among computer users on the network

Copyright: The exclusive statutory right of authors, composers, playwrights, artists, publishers, and distributors to publish and dispose of their works for a specified period of time.

Coordinated framework for the *regulation of biotechnology: The* fundamental document that outlines the

roles, responsibilities, and policies of the Federal Agencies involved in biotechnology and its regulation; and that sets forth premises for guiding future policy (49 FR 50856-50907).

Cross-hybridization: The crossing of two plants of different species to produce fertile offspring; a rare phenomenon in nature.

Cultivar: A strain or variety of cultivated plant that is distinguished from others by one or more characteristics reproduced in offspring.

Deliberate release: Refers to the purposeful introduction of genetically engineered organisms to the environment, either in a small-scale field test or on a large-scale commercial basis.

Depository: A facility that accepts, maintains, classifies, and distributes cultures of microorganisms, viruses, cells, and other biological material.

Dicotyledon: The class of plants distinguished by having two seed leaves within the seed.

DNA (Deoxyribonucleic Acid): The molecular building block of genes; repository of genetic information in all organisms. The information coded by DNA determines the structure and function of an organism.

Domain knowledge: The knowledge base of a computer program.

Ecological risk assessment: In the context of biotechnology, a prediction, based on available scientific evidence and experience, of how a genetically engineered organism will behave in the environment after its release. See also *Risk assessment.*

Electrophoresis: Technique by which an electric current is used to separate molecules in a mixture.

Enzyme: Any of a group of proteins that mediate the chemical processes of organisms without themselves being destroyed or altered.

Estrus: The period during which a female animal is most receptive to sexual activity.

Estrus cycle: Reproductive cycle; includes ovulation, egg maturation, and the preparation of the uterus to receive fertilized eggs. The cycle is under hormonal control.

Evolutionary biology: Study of the changes overtime in *genotype* and *phenotype* of populations.

Exotics: Species accidentally or deliberately released into a completely new environment.

Expert system: Two-component computer program that mimics the reasoning process of a human expert. The knowledge-base component contains the expertise for solving a problem, often in symbolic rather than numeric form; the *inference engine* component tells the program how to combine domain knowledge to do the task at hand. Expert systems are examples of *knowledge-based systems.*

Food additive: Any substance that becomes a component of food, or affects the characteristics of food; in the broadest sense, the definition would include new crop varieties developed either through traditional breeding or with biotechnology.

Food grades: Standards used to classify food products according to certain quality characteristics. Use of USDA *grade standards* is voluntary.

Full-text retrieval systems: A human-computer interface by which users can search a collection of documents for relevant information; especially useful for accessing a collection of documents by different authors who may use different wording to express the same thing.

Fungi: A group of simple plants without chlorophyll.

Gene: A discrete segment of a chromosome, made up of an ordered sequence of DNA molecules; the basic fictional unit of heredity.

Gene flow: The movement of genes in the environment. See Gene *transfer.*

Gene probe: A molecule of known structure and/or function used to locate and identify a specific region of a genome.

Gene stability: A measure of the effectiveness and persistence of a gene artificially introduced into an organism.

Gene transfer: The movement of a gene between different organisms. Natural processes of gene transfer include processes such as transformation (cellular uptake of naked DNA); transduction (virus-mediated transfer of a gene between bacterial strains); conjugation (direct genetic exchange between two bacterial cells); and pollen-mediated gene transfer. Concern exists that a gene artificially introduced into an organism with biotechnology could be passed to other organisms by one or more of these gene transfer mechanisms.

Genetic engineering: See *Recombinant DNA.*

Genome: The complete set of genetic material possessed by each organism, which is carried and passed to offspring in the germ (reproductive) cells.

Genotype: The hereditary makeup (genetic constitution) of an individual organism, as distinguished from its physical appearance (phenotype).

Grass herbicides: Herbicides that attack grass plants (monocotyledons); will not harm broad leaf plants *(dicotyledons)* such as soybeans.

Hardware (computer): The electronic and mechanical components of a computer, including keyboard and other input devices, the central processing unit, etc. In contrast to *software.*

Herbicide-tolerant crops: Crops that can grow in the presence of herbicides that destroy or harm non-tolerant plants.

Hypertext: A method of connecting related information multidimensionally, allowing access in a nonlinear fashion; analogous to footnotes.

Ice-minus: A bacterium from which a functional gene coding for a protein that promotes the formation of ice crystals has been deleted.

Indigenous organism: Organism native to an area; opposite of exotic.

Inference engine: See Expert *systems.*

Integrated pest management (IPM): A diverse array of pest control strategies, the integrated use of which is based on ecological principles and knowledge. IPM can be thought of as a crop management system whereby pest populations are maintained at levels below those causing economic crop loss. May include pest scouting, *biological control strategies,* chemical controls, crop rotations, etc.

Integrated system: A software system that allows users to access different decision support tools in the same environment. The tools accessed might be operationally independent (lowest level of systems integration) or logically linked, allowing the user to go from one application to another with the same user interface.

Intellectual property law: Statutes that protect works of the mind as personal property; examples include *patent, copyright, trade secret, and plant variety protection* laws.

In vivo: Within the living organism.

In vitro: Outside the living organism and in an artificial environment such as a test tube.

Ketosis: A metabolic disorder that occurs in dairy cows when the need for glucose exceeds the production of glucose.

Knowledge-based systems: Computer programs with the capability of dealing with symbolic data and/or of mimicing an expert's reasoning process. See *Expert systems.*

Land-grant system: An educational system established in 1862 with the passage of the Morrill Act, which made grants of land to States for creating universities that would fulfill the mission of providing higher education to the masses, with particular emphasis on the children of farmers and industrial workers.

Large-scale release: See *Deliberate release.*

Mainframe computers: Large, centralized computers with millions of logic circuits.

Marker genes: Genes coding for specific characteristics, the expression of which is used to distinguish genetically transformed cells or plants from untransformed cells or plants (i.e., antibiotic resistance genre).

Mastitis: An infection of the udder, the most common and one of the most important diseases affecting the milk cow.

Mathematical modeling: Construction of a mathematical framework to describe a process and predicts its outcomes.

Mesocosms: Contained walk-in chambers, the environmental parameters of which can be controlled to model ecosystems.

Microbial contamination (of foods): The presence/growth of microbial organisms in food; some foodborne organisms are toxic and may cause human illness or death.

Microbial herbicides: Microorganisms, or products containing microorganisms that are pathogenic to plant pests; used for the *biological control* of pests.

Microcomputers: Personal computers, sized for tabletop use.

Microcosm (Soil): A laboratory-based model ecosystem designed to mimic and used to study natural environmental processes.

Microinjection: A technique used to insert genes from one cell into another cell.

Microorganisms: Organisms that can be observed only with the aid of a microscope, e.g., *bacteria, viruses, protozoans,* some algae and fungi.

Molecular techniques: Refers here to the use of biotechnology to transfer selected genes between plant species.

Monitoring: Spatial and temporal tracking of an object or process. Monitoring of genetically engineered organisms and of their introduced genes contributes to risk assessment and management, and expands ecological databases.

Monoclinal antibodies: Identical antibodieses that recognize a single, specific antigen and are produced by a clone of specialized cells.

Monocotyledon: The class of plants distinguished by having one seed leaf within the seed.

Natural language interface: A human-computer interface that allows users to query a database and retrieve relevant information using natural language rather than, for example, a hierarchical menu system.

Nematodes: A phyllum of invertebrate roundworms.

Object-oriented simulation system: A type of knowledge-*based system that* explicitly models the structure, rather than the behavior of a real system; each component of the real system is represented in the simulation by a unit (object) consisting of self-descriptive data and procedures for manipulating that data.

Organic food: A term that generally designates foods produced without manufactured chemical inputs such as pesticides and synthetic fertilizers; however, no precise definition exists.

Patent: A grant issued by the U.S. Government that gives the holder right to exclude all others from making, using, or selling the patented invention within the United States, its territories, and possessions during the term of the patent

Pest resistance: Characteristic of certain crop cultivars allowing them to tolerate *pests that* harm or destroy nonresistant cultivars.

Pesticidal plants: Plants that are pathogenic and hence resistant to one or more plant pests.

Pesticide residue: Trace amounts of pesticides in food products; foods with pesticide residues above federally determined tolerances cannot be marketed.

Phenotype: The physical characteristics of an organism.

Plant pest: Defined in the Federal Plant Pest Act as any living stage of: any insects, mites, nematodes, slugs, snails, protozoa or other invertebrate animals; bacteria, fungi, or other parasitic plants or reproductive parts thereof; viruses, or any organisms similar to or allied with any of the foregoing; or any infectious substances that can directly or indirectly injure or cause disease or damage in any plants or parts thereof, or of processed manufactured or other products of plants.

Plasmnid: A circular piece of DNA found in the cytoplasm (rather than in the chromosomes), and able to replicate independently of the chromosomes. Bacterial plasmids are used as vectors in techniques of genetic engineering.

Pleiotropic effects: Multiple changes in metabolism that result from a single genetic change.

Polymerase chain reaction: An enzymatic process for rapidly generating large amounts of genetic material from a trace amount.

Population ecology: The study of the dynamics and growth of populations.

Population genetics: The analytical study of the properties of genes and changes in gene frequency overtime.

Porcine somatotropin (pST): See *Somatotropin.*

Primary gene product: A protein directly coded for by a gene; may be the final active product or may act as an enzyme or hormone that mediates the production of secondary gene *products.*

Prior art: That which is already known or available; one of the criteria used in evaluating patent applications.

Promotors: Regulatory genes that control the functioning of other genes.

Protozoa: A phyhun of unicellular or acellular microorganisms widely distributed in aquatic and wet terrestrial habitats; includes many parasites.

Recombinant DNA: Abroad range of techniques involving the manipulation of the genetic material of organisms, including technologies by which scientists isolate genes from one organism and insert them in another organism. The term is often used synonymously with genetic *engineering,* and to describe DNA sequences isolated from and transferred between organisms by genetic engineering techniques.

Restriction enzymes: Certain bacterial enzymes that recognize specific short sequences of DNA and cut the molecule at these sites; used to isolate specific genes of interest.

Restriction fragment length polymorphism (RFLP): A technique for mapping approximately where on the genome a specific gene(s) of interest resides.

Risk assessment: A scientific analysis of the potential risks and risk levels (quantitative or qualitative) associated with a particular action; includes estimates of possible health, environmental and other effects, and of the degree of uncertainty in these estimates. See also *Ecological risk assessment.*

Risk management: In this report, scientific and agronomic methods used to minimize the ecological risks potentially posed by deliberate releases of genetically modified organisms into the environment.

Robotics: Computerized machines that can be programmed to perform a variety Of labor-intensive tasks i,e., harvesting in agriculture.

Science-based regulations: Regulations (for genetically engineered organisms) based on scientific assessments of the risks posed by releasing such organisms into the environment.

Secondary gene product: A compound the production of which is mediated by primary gene products.

Sensor technology: Means by which some electronic systems monitor the environment combined with knowledge-W decision support systems, a potentially important management tool for fanners.

Small-scale field tests: See *Deliberate release.*

Software (computer): The programs and data in a computer. In contrast to *hardware.*

Somatotropin: A protein hormone produced by the mammalian anterior pituitary gland that affects growth and other physiological processes (i.e., lactation in dairy cows). Species limited Examples include human *somatotropin, bovine somatotropin, porcine somatotropin, and ovine somatotropin. Natural* levels of Somatotropins in agricultural animals can be elevated using genetic engineering techniques to increase production.

Suicide genes: Genes that effectively cripple or kill recombinant DNA-modified organisms following their intended use; a means of containing such organisms such that they cannot become established and spread.

Superovulation: The shedding of abnormally large numbers of eggs.

Systematic: The analysis of variation of different levels of taxonomic organization, with the ultimate goal of taxonomic classification; also used to monitor biotic diversity.

Tissue culture: A technique in which portions of a plant or animal are grown on an artificial culture medium.

Trade secret: Protection for information used in one's trade or business that provides a competitive business advantage over those lacking the information.

Transgenic animal (plant crop): Animal (plant, crop) whose hereditary DNA has been augmented by the addition of DNA from a source other than parental germplasm using genetic engineering techniques.

Vector: A carrier or agent used to introduce foreign DNA into host cells. Plasmids, bacteriophages, and other forms of DNA commonly are used as vectors in genetic engineering.

Veterinary biologics: Living organisms or their parts used by veterinarians to prevent *disease and/or promote animal health, e.g., sera, vaccines, veterinary growth hormones.

Appendix C
Commissioned Papers and Authors

This report and the three reports that complete this series were possible in part because of the valuable information and analyses contained in the background papers commissioned by OTA. These papers were reviewed and critiqued by the advisory groups, workgroups, and outside reviewers. The papers are available through the National Technical Information Service.[1]

Emerging Animal Technology

***Genetic Engineering in** Animal Agriculture*
Howard Bachrach
Southhold, NY

Bovine Somatotropin: Review** of **an Emerging Animal Technology
Dale E. Bauman
Cornell University

An Emerging Agricultural Technology: Porcine Sornatotropin
***Terry* D. Etherton**
Pennsylvania State University

An Emerging Technology: Poultry Somatotropin
Colin Scanes
Cook College, Rutgers University

Effects of Beta-Agonists on the Food Animal Industry
Edward Veenhuizen and D.B. Anderson
Eli Lilly and Co.

Reproduction and Embryo Transfer
William **Hansel**
Louisiana State University

Transgenic Poultry
***John* Kopchick**
Ohio University

Transgenic Fish
***Dennis* A. Powers (Stanford University) and**
Thomas T. Chen (University of Maryland)

Transgenic Swine
Vernon Pursel
U.S. Department of Agriculture

Transgenic Ruminants
Caird Rexroad
U.S. Department of Agriculture

Animal Health
Bennie I. Osburn
University of California

Antibiotic Growth Promotants
Gary L. Cromwell and Karl A. Dawson
University of Kentucky

Steroid-Like Growth Promotants
Rodney Preston
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Environment and Animal Behavior
***Stanley* E. Curtis**
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Agricultural Animal Welfare Issues
***Andrew* Rowan**
Tufts University

Emerging Plant Technology

***Genetic Engineering in** Crop Agriculture*
Robert **Fraley**
Monsanto Co.

Genetic *Technology for Resistance to Insect Pests*
Michael Adang and Lois Miller
University of Georgia

Genetic Modification for Weed Control
Ganesh Kishore
Monsanto Co.

Genetic *Modification for Disease Resistance*
Sue Loech-Fries
Purdue University

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1 These commissioned papers will be available in the fall of 1992 from the National Technical Information service, Springfield, VA 22161, telephone (703) *4874650.*

Volume 2: A New Technological Era for American Agriculture—OTA Commissioned Background Papers:
Part A: Emerging Animal Technology
Part B: Emerging Plant Technology
Part C: Emerging Computer Technology
Part D: Agricultural Research and Technology Transfer
Part E: Food Safety and Quality
Part F: Economic and Policy Analysis

Biocontrol for Weeds
Raghavan Charudattan (University of Florida) and Lloyd A. Andreas (U.S. Department of Agriculture)

Pathogens for Insect Control
James Fuxa
Louisiana State University

Use of Parasites and Predators to Control Insect and Mite Pests in Agriculture
Marjorie Hoy
University of California

Microbial Biocontrol of Plant Diseases
Christen Upper and Susan S. Hirano
University of Wisconsin

Temperature and Water Stress
John Burke
U.S. Department of Agriculture

Plant Disease Management
J.A. Browning
Texas A&M University

Insect and Mite Management
George Kennedy
North Carolina State University

Evolution of Resistance by Weeds and Pests to Herbicides and Pesticides
Fred Gould
North Carolina State University

Exchange of Genetic Material Between Genetically Engineered Crops and Close Relatives
Carol Hoffman
University of Georgia

Emerging Computer Technology

Knowledge-Based Systems for Crops
Nicholas D. Stone
Virginia Polytechnic Institute and State University

Use of Expert Systems in Animal Agriculture
Michael Tomaszewski
Txass A&M University

Expert *Systems for Business Decision Making*
Steven T. Sonka
University of Illinois

Networks, Telecommunications, and *Multimedia Information Bases for Agricultural Decision Support*
Jerry R. Lambert
Clemson University

Emerging Agricultural Technologies in Human-Computer Interactions
Lawrence R. Jones
Cornell University

Sensor Technology
Gerald W. Isaacs
University of Florida

Robotics and Intelligent Machines
Gaines E. Miles
Purdue University

Agricultural Research and Technology Transfer

The Changing Budget Environment for Agricultural Research and Technology Transfer
Susan Offutt
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The Changing Technology Environment
william Marshall
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Agricultural Research Issues for the 1990s
Terry B. Kinney
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Technology Transfer Issues for the 1990s
Jerome Siebert
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The Competitive Environment for Agricultural Research and Technology Transfer
Luther Tweeten
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Alternative National Agricultural Research and Technology Transfer Policies
Ronald Knutson
Texas A&M University

Privatization of Agricultural Research at Land Grant Universities
Edward Schuh
University of Minnesota

Food Safety and Quality

Biotechnology in Food Processing in the 1990s
Susan Harlander
University of Minnesota

Scientific Information and Methodologies for Assessing the Safety of Genetically Engineered Foods and Feeds
Ian Munro (Canadian Centre for Toxicology), Michael Pariza (University of Wisconsin), and Kent K. Stewart (Virginia Polytechnic Institute and State University)

Public Perceptions of Food Safety Risks: Implications for Emerging Agricultural Technologies
Eileen vanRavenswaay
Michigan State University

An Analysis of the Pork Grading System: Implications of New Growth Promotants
James Kliebenstein, Marvin Hayenga, Lauren Christian, Kenneth Prusa and Robert Rust (Iowa State University); John Forrest, Allan P. Schinckel, and Max D. Judge (Purdue University)

Assessing Federal Grade Criteria for Fruits and Vegetables
Thomas **Sporleder, Carl R. Zulauf, Rebecca Boerger, Mark Bennett, James Hoskins, Eugene Jones, Timothy Rhodus, Kurt Wiese**
Ohio State University

Economic and Policy Analysis

Adoption of Bovine Somatotropin: A National and Regional Analysis
J. Thomas McGuckin
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National and Regional Impacts of Bovine Somatotropin Adoption Under Alternative Dairy Program Policies
Derrell S. Peel
Oklahoma State University

Farm Level Impacts of Bovine Somatotropin Introduction and Adoption Under Alternative Farm Policies
James W. Richardson
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Farm Level Impacts of Porcine Somatotropin Introduction and Adoption on Representative Grain-Hog Farms in the Midwest
James W. Richardson
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Appendix D

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