November 10, 1999

Food safety — GMO's

ACTION

MEMORANDUM FOR THE PRESIDENT

FROM:

REF: **Decision on Agricultural Biotechnology Issues**

Purpose: A vigorous debate is under way in the U.S. and around the world about how governments should most appropriately regulate foods and crops made using biotechnology. This memorandum is intended to present the issues surrounding the current debate and provide policy options.

Background

Modern biotechnology or bioengineering refers to the use of recombinant DNA and related technologies to alter the genetic makeup of living organisms. These techniques allow scientists to identify and isolate genes of interest from any organism and put them into any other organism, as well as to introduce targeted genetic changes in organisms. The practical effect is to open up vast opportunities for developing new foods with beneficial characteristics such as pest and drought resistance, higher yield, enhanced nutrition and better taste. The United States is the acknowledged world leader in the biotechnology industry. Although the use of biotechnology for producing new drugs and vaccines has been widely accepted around the world, the use of the technology in producing foods has been much less well-received. Indeed, some consumer activists have alleged that these foods are unnatural, calling them "Frankenfoods."

In 1986, the Office of Science and Technology Policy published the "Coordinated Framework for Regulation of Biotechnology," in which the Food and Drug Administration, the U.S. Department of Agriculture, the Environmental Protection Agency, the Occupational Safety and Health Administration, and the National Institutes of Health described their policies for regulating research and products of biotechnology. The underlying premise of this policy was that, based on the government's assessment of the science, the regulatory framework pertaining to traditional genetic manipulation remains adequate for research and products of these newer techniques, and that no new laws were needed. As a result:

- USDA promulgated regulations requiring developers of bioengineered crops to notify it before planting such crops in the field. This process was intended to minimize any potential "plant pest" risks that the bioengineered crops might pose to agriculture and the environment. If USDA determined from its review of the resulting data that the crop posed no plant pest risk, it would classify the crop as a non-regulated article and allow it to be planted with no subsequent USDA involvement.

- FDA promulgated no new regulations but did publish a statement of policy indicating that new substances bioengineered into foods would be subject to premarket approval as food additives if

those substances differed significantly from substances commonly found in the diet. It went on to note, however, that most, if not all, substances being considered for introduction into foods through bioengineering were substantially the same as other substances found in the diet and therefore would not need premarket approval. FDA encouraged firms to consult with it on safety issues prior to marketing, which firms have been doing.

- EPA promulgated rules for the regulation of "intergeneric" microbes, as potentially toxic new chemicals, and for the regulation of pesticidal substances introduced into plants. EPA examines both environmental and human health risks of the microbes and pesticides.

Federal regulatory agencies remain confident that bioengineered crops and foods sold in the U.S. are safe. Bioengineered corn, soybeans, cotton and canola are widely grown and consumed in foods here, and American consumers retain a generally benign view of the technology. Nevertheless, companies are increasingly concerned that public acceptance could erode in the face of media questions and activists' representations that the technology poses unknown long-term risks. And they fear that international resistance to the products, especially in Europe, could eventually spill over into the US market.

International Considerations. The EU is proving increasingly problematic, in part due to recent food safety scares unrelated to biotechnology as well as preliminary research indicating that some biotech corn pollen may harm Monarch butterflies. Last June, the EU Environment Council decided to require that agri-biotech products be proven to have no environmental or health risks before being placed on the market and that the EU Directive regarding biotechnology regulation (90/220) be revised to include additional procedures for handling already-approved biotech seeds and bulk commodities. US producers are being adversely affected by this effective moratorium on regulatory approvals of bioengineered products. With seven pending applications for new corn varieties, corn growers are losing at least $200 million per year in exports. US producers are concerned that additional countries, such as Japan, Korea, Australia, and New Zealand, are following the EU's lead in mandating labeling of biotech foods, as foreign food retailers and processors are beginning to demand GMO-free foods to protect their brand image and avoid loss of market share. This is generating uncertainty among American farmers and concern about the added segregation and testing costs. As a result, the Administration is working to promote fair market access for US exports on several fronts, including:

- Technical cooperation and information sharing in the OECD and Transatlantic Economic Partnership in projects initiated at this past June's G-8 and US-EU Summits as well as through the National and Royal Academies of Science;

- A high-level US-EU governmental dialogue that was initiated in your recent meeting with EU Commission President Prodi for the purpose of securing more predictable regulatory approval processes in Europe and resolution of outstanding market access issues, including blocked US corn exports; and

- Preparation of US negotiating objectives for the Seattle WTO Ministerial aimed at focusing any discussion about biotechnology in the new trade round on ensuring the continuing application of existing trade disciplines to biotech trade and promoting greater predictability to regulatory approvals based on sound science.

Domestic Perspectives

- Government. The U.S. Government (USG) position on labeling of genetically engineered or modified agricultural crops and products has been to oppose any mandatory labeling of such products. This position is based on the Food & Drug Administration's conclusion that genetically engineered foods are substantially equivalent to their conventional counterparts. However, the FDA requires labeling of food, including that which is bioengineered, whose composition has been significantly altered, whose nutritional values or intended use is different from conventional food, or which has allergenic properties. While this interpretation and policy is based on sound science, it has not entirely succeeded in quieting consumer demands for labels and other information about the bioengineered content of food.

- Consumers. Although US consumer perceptions of agri-biotech products remain largely positive, the situation is fluid. In its September 1999 edition, *Consumer Reports* magazine advocated labeling of bioengineered food products. And US advocacy groups are intensifying media and public education campaigns. Some contend that bioengineered foods should be subject to formal FDA safety approval before being marketed, labeled as bioengineered, and examined more thoroughly for potential environmental risks. A number of them filed a lawsuit last year against FDA, alleging that it is violating the law by not requiring such labeling and premarket approvals. Another lawsuit has been filed against EPA, alleging that its oversight of certain pesticidal substances in bioengineered crops and foods is inadequate.

- Industry. For its part, industry has not reached a consensus on what direction the U.S. should take to address the problems of labeling and segregation. Food processors and their trade organizations (e.g. Grocery Manufacturers Association, National Food Processors Association) are opposed to the labeling of GMO's for exports mainly because of the increased costs and their fears that eventually they would be required to label domestic GMO food products as well. However, they have recently begun quietly suggesting that some degree of greater engagement by the government would be desirable, including additional public education, a requirement that companies notify FDA of new bioengineered products before marketing them, and work by USDA and FDA to help farmers, companies, and consumers determine what constitutes a non-biotech product.

- Farmers. Perhaps the most pressing aspect of the issue is the uncertainty facing farmers, who fear development of a two-tier price system with discounts for biotech crops and a shortage of conventional seeds next spring. Many of our farmers in recent years switched to bioengineered crops because of their enhanced traits, reduced costs of pest/disease control, and environmentally friendly attributes. However, growing demand for non-GMO commodities is expected to add costs due to segregation and handling, in the range of 12% to 17% more for non-GMO bulk commodities. This figure could increase substantially if very stringent thresholds were adopted by countries and companies (e.g., the EU has recently proposed that any product containing more than 1% of bioengineered product be considered bioengineered), suggesting that the US has a major commercial stake in how such decisions are made.

- Environment. Finally, agricultural genetic engineering could have significant environmental impacts, both good and bad. Potential benefits include reduced pressure to clear tropical rainforests for farmland (due to enhanced agricultural productivity), quicker, more effective clean-up of oil

spills (with genetically engineered plants and microorganisms) and less use of harmful pesticides. Risks include the development of "super-weeds" (if genetically modified plants hybridize with wild relatives), adverse impacts on non-target species (such as the monarch butterfly) and disruption of ecosystems (for example, by the unintended release of "super-growth" salmon into the marine environment). In several recent cases, agencies have identified environmental risks from GMOs and responded accordingly. In 1997, EPA expressed concern about hybridization of certain genetically-modified cotton crops with wild relatives in certain parts of Florida and Hawaii, and denied approval for planting in those areas. EPA is currently considering guidelines to protect monarch butterflies in the planting of Bt corn. In other cases, the regulatory authorities for addressing environmental impacts of GMOs may be less clear. FDA, for example, is currently considering applications for the approval of genetically-modified salmon that grow faster and larger than native species. Although FDA is considering the ecosystem impacts of an unintentional release of the modified salmon as part of a NEPA review, it is not clear that FDA's legal authorities would allow the agency to deny approval based on adverse ecosystem impacts if any were found.

Options

An NEC High-Level Group on Biotechnology was created last spring to assess these developments and consider their implications for public policy. Principals, Deputies and staff have met and conducted outreach with the producer and NGO communities. Following are policy options that have emerged from this process for your consideration:

1. Enhancing Public Education and Outreach to Strengthen US and Foreign Consumer Confidence

- Domestically, engage in greater outreach to emphasize the scientific basis of US regulation and convene public sessions and meetings for the purpose of soliciting broad public and scientific input on whether additional regulation (for food safety, food labeling, environmental safety) is appropriate. Panels also could be set up to provide a forum for discussing non-scientific (e.g., cultural and social) issues of public concern.

- Encourage US food processors to post on Federal or their own web-sites listings of products containing bioengineered ingredients, with information about their safety and the Federal procedures through which they passed.

- Intensify international educational, cooperative scientific, diplomatic, and technical assistance activities to explain US regulatory policies and work toward more consistent policies.

These activities would enable the regulatory agencies to hear public concerns, receive scientific input, dispel inaccurate information, and influence regulatory decisions in foreign markets. All agencies are supportive of these steps, and many, including USDA, FDA, and State, are undertaking them presently.

2. Maintaining and Strengthening Confidence in the US Regulatory Framework

a) Require Companies to Notify FDA 90 Days before Biotech Products Are Introduced into Commerce. In 1992, FDA issued a policy statement to provide industry with guidance on Federal requirements that must be met before feed and food products derived through recombinant DNA

techniques can be introduced into commerce. This policy statement did not mandate pre-market notification or approval, but encouraged consultations between industry and FDA. To date, all new feed/food products have gone through this voluntary consultative process; however, critics point to the voluntary nature of this process to make the claim that FDA's oversight of GMO food is based on an honor system. In an attempt to address this criticism, FDA has launched a series of public listening sessions over the next month in part to explore the possibility of requiring pre-market notification.

This step would provide an added level of assurance that government is aware of all products marketed and that all regulatory questions are answered prior to marketing. It would build public confidence in FDA oversight, responding to criticism that current system is an honor system in which industry voluntarily engages FDA in its safety evaluation, and possibly provide an opening to work in a more cooperative fashion with the Europeans on biotech issues. At the same time, it would not directly address the principal criticism that bioengineered foods are not subject to mandatory premarket approval and may provide ammunition to opponents of the technology, who may portray this requirement as evidence that bioengineered foods pose special risks not associated with other foods.

All agencies are generally supportive; however, FDA believes that any policy change in this regard should be based on and follow a process of public outreach, such as its three public sessions scheduled over the course of the next month.

b) Direct CEQ to Organize an Interagency Process to Examaine the Adequacy of Federal Environmental Monitoring Activities and Regulatory Authorities with Respect to Agricultural Biotechnology. This proposed process would look at the adequacy of our environmental monitoring activities and capabilities as well as the sufficiency of the existing regulatory authorities and framework. Analysis would begin with case studies of how the existing system applies to different transgenic organisms. Work would be designed to identify strengths and weaknesses of the current system and, in combination with scientific information, establish a foundation for future recommendations. New directions might include recommendations for additional environmental monitoring and risk assessment activities. Initial recommendations would be likely within six months. This policy option would help address questions about the environmental implications of agricultural biotechnology and bolster public confidence that the federal government is taking them seriously. It is supported by all agencies.

3. Facilitating Voluntary Informational Labeling of Non-Biotech Products (i.e., defer to the private sector on product segregation and labeling but engage with it to lend order to the process and reduce uncertainty and confusion for farmers, companies, and consumers).

Although there is general confidence in and out of government that bioengineering *per se* does not pose unique health risks in food products requiring FDA-approved labeling, consumer preferences abroad and, to a lesser extent, in the US are prompting some commodity firms and food companies to segregate and voluntarily label non-bioengineered crops and products. Competing producers have an interest in ensuring that such claims are not false or misleading. Consumers have an interest in ensuring that information voluntarily disclosed on products is accurate, reliable, and comparable to information found on other products, as illustrated by the current confusion of supermarket shoppers in the UK. Finally, farmers and elevator operators have an interest in ensuring that steps they take to test

and maintain the segregated identity of non-biotech crops will be reliable and generally recognized as valid by commodity firms. Accordingly, this option would launch a process of public outreach and technical research through USDA and FDA to support an orderly process of voluntary product segregation and labeling to the extent one emerges in the private sector.

a) USDA process on testing, tolerances, and quality assurance. USDA would initiate a comprehensive process of public outreach to determine the feasibility of establishing standardized testing protocols, maximum-biotech content tolerances, and quality assurance programs to support voluntary non-biotech product segregation and claims. This process would take into account both consumer demands and production and handling factors such as pollen drift and commingling. It would involve public meetings, specific stakeholder group consultations, and the issuance of an Advanced Notice of Proposed Rulemaking (ANPR). It might most usefully be initiated following next year's harvest after the industry has had more experience with segregating and testing commodities. Once a certification process were established, the GMO status of a given commodity would become a key component of industry-developed "chain of custody" programs, which might facilitate voluntary labeling of consumer products. This USDA process would also inform and support USG efforts to influence foreign regulatory decisions about non-biotech tolerance levels and preserve fair market access opportunities for US farm exports. Should domestic industry choose to use such labels, FDA would need to determine whether the labels were truthful and not misleading.

b) FDA process to develop guidance for voluntary informational labels.

The Food and Drug Administration (FDA) has already initiated a Federal Register notice announcing three hearings on November 18 and 30 and December 13. The purpose of these hearings is to share the agency's approach regarding safety evaluation and labeling of food products derived from bioengineered plant varieties, to solicit views on whether FDA's policies or procedures should be modified, and to gather information on the most appropriate means of providing information to the public about these products. Under current Federal Food, Drug, and Cosmetics Act (FFDCA) authority, companies currently can use product labels to indicate whether their products contain genetically engineered ingredients. However, the labels must meet the standard of being truthful and non-misleading, as interpreted by the FDA. Building on the current FDA hearings, this policy option would create a process by which the agency would develop guidance on the elements of a truthful and not misleading label for non-GMO food products in order to inform the design of any such claims voluntarily made by companies.

USDA and other agencies support these options, with the exception of HHS, which believes that even limited governmental involvement in activities related to biotech labeling would implicitly bless and energize the actions of those who oppose the products and call for their mandatory labeling, thereby undermining public confidence in them. HHS is also concerned that adding information on food labels on matters unrelated to the safety or fundamental characteristics of the product would undermine the function and utility of food labels, in part by adding clutter and distracting consumers from core nutritional information.

4. Supporting Mandatory Pre-Market Approval and Product Labeling

The Administration could adopt the EU posture of requiring pre-market regulatory approval and labeling of products with bioengineered content above a certain threshold. It could do so by sponsoring or endorsing legislation in Congress.

a) Mandatory approval of new products (as distinguished from mandatory pre-market *notification* in Option 2a above) would allow FDA itself to vouch for safety of bioengineered foods based on in-depth reviews, as it now does for food additives. This would satisfy demands of at least some consumer groups by providing an additional assurance of safety, removing the criticism that the current system depends on the good faith of biotech companies. However, such a change in policy would be opposed by industry on the grounds that it could undermine public confidence by suggesting that the federal government has serious concerns about the safety of the technology. It could also create significant period of "regulatory limbo" between the time of the proposal and enactment, delaying market entry of commercially important new foods despite the longstanding Federal view that bioengineered foods do not raise scientific or safety issues warranting such oversight.

b) Mandatory labeling of bioengineered food products may ultimately be the only way to cease being on the defensive about bioengineered foods, because many consumers may decide to distrust the technology until they feel that they have the capacity to choose it or not. In light of the number of bioengineered crops grown in the U.S., many processed foods would need to be labeled, thereby potentially eliminating any stigma associated with labeled products. By taking this posture, the Administration might be able to get in front of the issue, forcing stakeholders to work with Congress to develop a solution. This option would afford the maximum degree of information to consumers. With access to information readily available, their concerns over the technology might well be lower in the long run than in the absence of a regime of mandatory product disclosure.

On the other hand, mandatory food labels for biotech content could undermine the function and utility of the food label, whose purpose is to provide information pertinent to characteristics and composition of the food. As such, it could distract attention from important nutritional and health information now on food labels and trigger additional calls for consumer "right to know" labeling on other issues. In addition, an abrupt policy shift of this nature could foster greater distrust of bioengineered foods by giving the impression that they must be different and riskier than other products, leading food processors to avoid their use and consumers to boycott their purchase. Since industry is currently interested most of all in having the federal government clearly and repeatedly vouch for the safety of the products, it would undoubtedly be highly critical of this policy and consider fundamentally inconsistent with long-standing government position that biotech foods are as safe as their non-engineered counterparts and as a class have no distinguishing characteristics that would warrant labeling.

No agency supports these options, reflecting the concern, shared by industry and farmers, that such a major policy shift might alarm consumers and create a disorderly shift in their purchasing behavior that would not be warranted by our scientific understanding of the issue. The top priority of industry and farmers is for the USG to take steps to reinforce the generally strong level of consumer confidence that still prevails in the US. They perceive that these steps would work at cross purposes to this objective.

RECOMMENDATION

Approve

Option #1 -- Enhancing Public Education and Outreach to Strengthen Consumer Confidence.

Option #2 -- Maintaining and Strengthening Confidence in the US Regulatory Framework by:

a) requiring companies to notify FDA 90 days before biotech products are introduced into commerce; and
b) directing CEQ to organize an interagency process to examaine the adequacy of federal environmental monitoring activities and regulatory authorities with respect to agricultural biotechnology.

Option #3 -- Facilitating Voluntary Informational Labeling of Non-Biotech Products by initiating:

a) USDA process on testing, tolerances, and quality assurance; and
b) FDA process to develop guidance for voluntary informational labels.

Option #4 -- Supporting Mandatory Pre-Market Approval and Product Labeling

Attachments

Tab A Memorandum to NEC High-Level Group Principals

FYI —
IF YOU WANT TO GO

TO: DISTRIBUTION

FROM: Sharon Yuan, NEC

Attached is the agenda and background paper for tomorrow's (September 30, 1999) deputies meeting on Biotech in Room 248 from 9:00 - 10:30 am. Deputies plus one are welcome.

Thanks.

FOOD SAFETY —
GMO's

DEPUTIES MEETING ON BIOTECHNOLOGY
Environmental Safety of Genetically Engineered Organisms
September 30, 1999; 9:00 –10:30 am
Room 248 OEOB

AGENDA

I. Plants

- Monitoring Options

  -- Adverse effects reporting
  -- Voluntary plans
  -- Mandatory plans
  -- Comprehensive monitoring programs

II. Fish, Insects, and Microorganisms

ENVIRONMENTAL SAFETY OF GENETICALLY ENGINEERED ORGANISMS

This paper is designed to provide the NEC Deputies with background on the major environmental safety considerations that inform risk assessments on genetically engineered plants and other organisms, such as fish, insects, and microorganisms. Since possible negative environmental impacts resulting from the use of genetically engineered crops are a major area of concern, Part I of this paper provides expanded treatment of safety issues associated with crops. Part I also presents options for how we might monitor possible environmental effects. Part II provides a general overview of environmental safety issues associated with genetically engineered fish, insects, and microorganisms used in commerce.

PART I: PLANTS

Traditional breeding practices and underpinning science

Plants used in agriculture have been genetically modified for centuries. Although unaware of the underlying genetic mechanisms, ancient farmers were able to introduce many mutant genes and novel gene combinations in early-domesticated crops, such as wheat, rice, and corn, by selecting plants with desirable characteristics. Following the rediscovery of Gregor Mendel's famed pea studies, scientists established plant-breeding programs in the early part of this century. Modern plant breeders introduce into crops numerous genes conferring traits such as disease and pest resistance, agronomic characteristics (e.g., plant structure and salt tolerance), and food quality attributes (e.g., changes in oil and protein composition).

Depending on the species, there are approximately 20,000 to 50,000 genes in a crop genome (a genome is the total complement of an organism's genetic material or DNA). Many of these genes are the same in plants, animals, and even microorganisms. These are usually referred to as housekeeping genes, which perform various functions common to all forms of life. Other genes may be unique to a certain plant, such as corn, or be highly variable from plant to plant. Plant breeders attempt to optimize for a specific purpose (e.g., pest resistance) the performance of the plant's existing complement of genes and incorporate additional genes usually from plants that are sexually compatible with the crop. Using laboratory techniques, breeders have also utilized to a limited degree genes from plants that are not sexually compatible with the crop. Due to the lack of precision of traditional breeding methods, plant breeders typically transfer thousands of genes in every hybridization event. Many, if not most, of these genes are of unknown function, and some of these genes may result in the production of substances harmful to human health or the environment. Breeders must go through many generations of back crosses to the parent crop to eliminate as many unwanted traits (and therefore genes) as possible.

Plant breeders select plants containing desired gene combinations by intensive screening through field trials and laboratory testing. Typically, it takes many years (~10) for a new variety to be ready for commercialization. During that time, traits are monitored, genetic stability is assured, and in some cases when known toxicants might be present, food safety studies are conducted. The exact path a breeder takes to develop a new variety depends on the crop's biology.

Breeding technology has been the driving force behind increases in agricultural productivity. New varieties are continually needed to satisfy market demands for new types of products and to keep up with the rapid introduction and evolution of pests and diseases. Crop yields can be reduced by as much as 20% on average due to pests and diseases. Numerous varieties of each major crop are available to farmers in any one year. For example, there are over 300 varieties of wheat grown in the United States, each developed to withstand different local environmental conditions and fulfill specific market needs.

Plant breeding has been a practice conducted mostly by public sector institutions such as State Agricultural Experiment Stations and by seed companies. Oversight of the products of plant breeding has been largely left to breeders, crop committees, and others that certify the purity, uniqueness, and, in some cases, the safety of new varieties. New plant varieties, whether developed with new or traditional breeding techniques, routinely undergo many years of testing and evaluation prior to commercialization to determine that the plants behave as expected under various environmental conditions. Federal oversight of the products of plant breeding has been minimal.

In the early 1980s, plant scientists, utilizing the natural ability of the common plant pathogen *Agrobacterium* to insert its genes into the genes of plants, began developing procedures that allow any gene from any species to be inserted into a plant's genome. Once modified to resemble a plant gene and inserted, new genes from non-sexually related species behave as would the plant's own genes--they are passed on to offspring and become part of the plant's gene pool from which breeders can draw for new and useful traits.

The world's leading scientists have determined that there is nothing inherently dangerous about the *process* of genetic engineering or, as called in Europe, genetic modification. Clearly, new genetic combinations can be created that may pose a risk to the environment or human health (the same can be said for products of more traditional breeding too). Thus, our nation's existing statutory framework, established to deal with these risks, was determined in the mid-1980s to provide appropriate authority for regulating these products (the Coordinated Framework for Regulation of Biotechnology). Based on our extensive knowledge base of crop plants, past breeding practices, and experience with laboratory uses of genetic engineering, the concept of a new "gene law" was rejected and regulations were promulgated under existing authorities to provide additional assurances that those products that might be harmful to the environment or human health would be reviewed before field testing could begin or commercialization allowed.

The decision to rely on existing statutes for biotechnology oversight and build upon the credibility of the existing regulatory infrastructure was probably the largest factor in our ability to advance this technology so quickly. This set the stage for a robust public and private sector R&D effort leading to a full pipeline of genetically engineered plant varieties. We now have 13 years experience in evaluating plant biotechnology products.

Environmental Issues

USDA/Animal and Plant Health Inspection Service (APHIS) and EPA have primary responsibility for overseeing the environmental safety of genetically engineered crops. Primarily under the authorities of the Federal Plant Pest and Plant Quarantine Acts, APHIS is responsible for protecting U.S. agriculture from the possible harmful effects from genetically engineered plants that might present new plant pest risks. APHIS' responsibilities under the National Environmental Policy Act require them to also assess a broader set of environmental issues and impacts on the environment in general along with social and economic effects. APHIS is currently assessing its compliance with NEPA.

The Federal Insecticide, Fungicide, and Rodenticide Act gives EPA the authority to assess the environmental and human health risks associated with crops containing genes that render them resistant to insect pests and pathogens (e.g., *Bacillus thuringiensis* insecticidal proteins produced in corn – Bt corn). This statute also gives EPA authority to assess risks associated with herbicides, such as herbicide resistance traits in plants. Finally, FIFRA gives EPA both pre-market and post-market authorities, e.g., EPA has imposed resistance management conditions that must be adhered as a condition of registration. EPA also has the authority to regulate new chemical substances produced by genetically engineered plants through the Toxic Substances Control Act.

Weediness: Weediness concerns have been raised on two fronts. First, there is concern that genetically engineered crops will become weeds. The second concern is that genetically engineered traits will spread from crops to closely related wild weed species, enhancing weediness of the wild relatives. These same concerns are also relevant to traditionally developed crops. Both APHIS and EPA look carefully at these potential risks. Care is taken to assess the geographic distribution of weedy relatives of genetically engineered crops and to limit, to the extent possible, gene flow through pollen from crops to weedy species. In the United States, the vast majority of our crops is derived from non-native plants and, therefore, presents little opportunity for genes to be transferred from crops to weed species. Some crops, such as sunflower and cotton, have weedy relatives in the United States and do present additional regulatory challenges. For example, EPA restricts the production of Bt-cotton in Florida and Hawaii where sexually compatible wild cotton relatives can be found. Breeders identify and eliminate plants from their field trials that exhibit excessively weedy characteristics through extensive field trials. It is also generally true that weediness is a complex of traits rather than the result of a single gene.

Adverse impact on non-target species: APHIS and EPA are concerned about adverse impacts on non-target species. This is an issue that is handled on a case-by-case basis and is dependent on the crop's biology, its use, and the specific environment in which the crop will be grown. The recent report on the possible impact of Bt-corn pollen on monarch butterflies is an example of a non-target impact. Regulatory agencies evaluate likely possible non-target impacts before a plant is field tested or commercially released. The ability to predict all possible non-target impacts is an unrealistic expectation for regulatory agencies, since available data do not fully describe the complex interactions between any species and its surrounding environment. When additional data become available or new concerns are raised, as in the case of the monarch butterfly, regulatory agencies reassess the science and take action as appropriate. On proposed approach to manage the impact of corn pollen that contains the Bt pesticidal protein is to utilize buffer areas between cornfields and areas that contain milkweed. The buffer acts a barrier milkweed population thereby reducing the likelihood that monarch caterpillars will come into contact with sufficiently high concentrations of pollen to cause high levels of caterpillar mortality. Data are still being gathered to determine if planting Bt-corn without buffers is having a significant negative impact on populations of monarchs.

Creation of new or more serious viral diseases of plants: This concern stems from the fact that one of the strategies used to control plant viruses is to insert plant viral genes into plant DNA. This procedure "immunizes" the plant, so it will resist infection. This procedure exploits the long-practiced virus control strategy of deliberately infecting plants with an attenuated viral strain to protect the plant from more virulent strains. To make the process more efficient, genetic engineers have selectively incorporated certain viral genes directly into the plant's DNA. Such an approach to disease control might increase the possibility that new viruses might be created through recombination events between the genetically engineered viral genes and other viruses that can overcome the resistance. The likelihood of such a recombination event has been the subject of considerable scientific investigation and deliberation. As a result, APHIS and EPA have developed regulations supported by the scientific community as reflected in reports by the Organization for Economic Cooperation and Development (OECD) and the American Institute for Biological Sciences (AIBS). To date, only resistance to viral diseases endemic to the United States has been commercialized, which further reduces the risk of recombination.

Development of Resistant Pests: The ability of pests and pathogens to overcome the protective nature of pesticides or host plant resistance genes is common. In modern agriculture, selection pressure for resistant pests and pathogens is intense. Thus, scientists and government regulators are well aware of the high probability that resistance to pest control genes, including those that are genetically engineered, will likely develop unless effective management strategies are used. USDA and EPA are working with industry, the scientific community, and some environmental groups to develop resistance management plans that limit the likelihood of resistance development to the insecticidal proteins obtained from the bacterium *Bacillus thuringiensis* or Bt. Part of this concern stems from the fact that Bt is used as a topically-applied microbial pesticide and is important to organic farmers. EPA already requires resistance management plans and

will modify this requirement to reflect the latest scientific evidence. The primary strategy that will be deployed by farmers to manage resistance development will be the use of refugia. For example, refugia are areas within a field that contain corn lacking the Bt pesticidal gene. Refugia reduce the selection pressure on pest and pathogen populations to develop resistance to the pesticidal gene.

EPA's Approach to Refugia, Buffers, and Upcoming Action. Given the concerns expressed above on pesticide resistance, EPA placed before the FIFRA Scientific Advisory Panel (SAP) and the Pesticide Program Dialogue Committee (PPDC) the question of whether EPA should use its authorities to develop and implement resistance management programs that limit the likelihood of resistance developing to the insecticidal toxins, Bt. Both groups advised EPA to use its authorities to limit the likelihood of resistance to Bt toxins developing in pest populations. EPA also held two public hearings (Washington DC and College Station TX) to collect information on resistance management. Although resistance to any pesticide can, and has, developed in pest populations, the attempt to manage on a large scale the emergence of resistance to Bt toxins is the first of its kind. When EPA placed resistance management requirements on Bt toxins engineered into plants, it recognized that the requirements would evolve as information accumulated. EPA began working closely with USDA, industry, the scientific community, and environmental groups to gather the information needed to develop resistance management plans prior to registration of Bt-crops, and continues these efforts today. EPA modifies its resistance management requirements to reflect the latest scientific evidence.

Resistance management plans are in general composed of several elements, including; generation of information on pest biology, deployment of sufficiently high doses of toxin to kill all susceptible pests, refugia (areas where some portion of the pest population can live without exposure to the pesticide in order that this portion of the pest population remains susceptible to the pesticide and passes this susceptibility to their offspring), monitoring for the emergence of resistance in the pest population, integration into Integrated Pest Management Programs (IPM), grower education and communication, and development of alternative pesticides with different modes of action. Of these elements, the implementation of refugia has required the most discussion and consideration. To gather information on resistance management in general and refugia in particular, EPA requested advice from its SAP in a 2 day meeting in 1998, and held in 1999 two workshops (Chicago IL and Birmingham AL).

Bt toxins have been commercialized to date in three crops: potato, cotton and corn. Based on market penetration analyses that suggested that Bt-corn would represent a small portion of the corn planted between 1996 and 2001, EPA did not place requirements for refugia on the initial Bt-corn registrations. However, farmers adopted Bt-corn more rapidly than anticipated, and to ensure some level of resistance management in corn, subsequent registrations contained refugia requirements. EPA is working towards creating a more consistent, level playing field for all companies registering and marketing Bt-corn, as well as attempting to develop effective resistance management plans for corn pests. To this end, the Agency has fostered and participated in efforts by stakeholders to

develop effective resistance management plans for corn pests. The effort for corn has been led by the USDA NC-205 group (research and extension entomologists of the North Central Regional Research Project).

Based on the NC-205 recommendation, EPA proposes to inform Bt-corn registrants that for the 2000 growing season with regard to refugia:

- When the corn plant is expressing a high enough dose of Bt toxin to kill almost all members of the pest population, for each farmer, 80% of the acreage planted to corn can be planted to Bt-corn. The 20% of the acreage planted with non-Bt-corn should not be sprayed with pesticide unless devastating pest infestations occur. If the farmer plans to spray with a pesticide, the farmer can plant 60% of the acres planted to corn with Bt-corn. 40% of the acres planted to corn should be planted to non-Bt-corn.

- When the corn plant is expressing a dose that is not high enough to kill almost all members of the pest population, higher percentages of the acres planted to corn should be planted to non-Bt-corn.

EPA also proposes that in light of concerns about potential adverse effects of Bt-corn pollen on Monarch butterflies, it might be prudent for farmers to consider for the 2000 growing season inserting a "buffer" between Bt-corn and areas where milkweed (food for Monarch caterpillars) grow. Buffers would be 30 or more feet wide if the field is 5 acres or less and 40 or more feet wide if greater than 5 acres. Buffers could be non-Bt-corn or any other crop. EPA is only suggesting that use of such buffers be considered until sufficient data are gathered to determine the effect of Bt-corn pollen on Monarch populations. EPA is not mandating their use.

Monitoring Environmental Impacts

Currently, there are no comprehensive monitoring plans designed to track possible environmental impacts of genetically engineered crops (or any crops for that matter). This is because regulatory agencies believe the existing regulatory framework provides appropriate assurance that biotechnology-derived crops are as safe for the environment as other crops. However, in some cases, monitoring would be beneficial to help guide best agricultural practices regardless of whether the practice is based on biotechnology (e.g., monitoring pest resistance to guide applications of pesticides). This section presents monitoring options that might allay concerns or guide future agricultural practices.

How to Monitor

There are two essential points that need to be considered when developing a monitoring plan: what to look for and how to look for it.

What to look for: This consideration seems self-evident on its face. However, what to look for is limited by what we know. It is difficult to create a monitoring system for outcomes that we cannot imagine. Technically speaking, monitoring can probably be

developed and implemented for many of the outcomes identified in the environmental risk section of this paper.

How to look for it: Having identified a concern that merits monitoring, the next challenge is to create a monitoring system to watch for possible outcomes. The following elements must be included in any monitoring protocol:

- Establishing the baseline: In order to observe any change in the behavior of a population of organisms, a "baseline" must be obtained. The facet of the environment most likely to be affected must be described prior to introduction of the genetically engineered crop. Therefore, the behavior of the non-modified crop in the environment is a critical baseline element for comparison.

- Choosing the number and location of sampling sites: Where to sample and how many sites to sample to give an accurate picture are important considerations. The greater the number of sampling sites, the more likely we are to obtain early indications of changes in the environment, but the higher the cost.

- Developing a timetable for sampling: The timing of sampling must be carefully determined. For example, in developing monitoring for the emergence of resistance in pest insect populations, some insect pests have several generations per season (summer). Others have only one or two. For insects that occupy a large range, e.g., from Mexico through the Dakotas, those in the southern part of the range may begin to emerge earlier than those in the northern part of the range. Those in the southern part of the range may also have more generations.

- Developing a standard approach to collecting specimens: A standardized approach is essential to obtaining specimens that will give statistically valid results. For example, with most caterpillars, only the youngest are sensitive to Bt toxin (earliest instars). Older caterpillars are resistant. Thus, which type of caterpillar (young vs old) is to be sampled is an important consideration. In addition, a statistically valid number of samples must be collected.

- Developing, standardizing, and validating test conditions: For example, in the case of monitoring for the emergence of resistance in pest moth populations to the Bt toxin from exposure to crop plants expressing Bt toxin, a large number of young caterpillars are exposed in the laboratory to the toxin at varying doses, and the percent of mortality determined. If the mortality response of these caterpillars is statistically different from the baseline response, a second series of tests will further quantify the concentration/mortality response. On the basis of this second test, follow-up actions may be indicated, e.g., intensified field surveillance in and around the collection sites or fact gathering to assess reasons for the response.

- Duration of monitoring: Decisions must be made on how long we should monitor to see whether a problem is going to develop. Since it may take quite a few years for a

problem to become apparent, consideration should be given to how to continue such monitoring over a number of years.

Monitoring Options (these are not mutually exclusive):

- **Adverse effects reporting**

This would require certain people (e.g., those using or associated with a genetically engineered crop) to report to a designated Federal agency if they have a suspicion that an adverse effect may be caused by a genetically engineered crop. The Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and the Toxic Substances Control Act (TSCA), administered by EPA, both have such provisions for pesticides and crop varieties they review.

The advantages of such provisions, in terms of monitoring, are that they are relatively cheap; those most likely to notice an unusual or an adverse effect (farmers or researchers in the field) can be called upon to forward their observations to the Federal agency; and unforeseen, unimagined events may well be reported. If the adverse effects reporting is a statutory requirement (as in FIFRA and TSCA), this type of monitoring will continue to occur no matter the Administration. The USDA is looking at its statutes and regulations for the ability to require monitoring after commercialization or to bring back under regulation commercialized products once adverse impacts have been documented.

The disadvantages are that the Federal agency may receive many extraneous reports that have nothing to do with adverse environmental effects, and guidance on what to report may be difficult to write and indeed counterproductive if the intent is to also pick up unforeseen, unimagined events. The effectiveness of adverse effects reporting therefore depends to a large extent on what the observer considers to be an adverse effect as well as motivation to report and training to detect adverse events.

Pros

--Would not require significant expenditure of funds to implement; and
--Statutory authority may already exist.

Cons

--Not comprehensive so certain impacts might go undetected;
--Environmental groups would likely find relying on adverse reporting inadequate; and
--Reporting motives might be questioned.

- **Voluntary plans**

Voluntary monitoring programs based on grants/contracts could be developed and funded to address certain concerns. Given the complexity of many of the monitoring considerations, and the potential size of areas monitored, multi-institutional

grants/contracts may be necessary. Organizations consisting of scientific professionals may also play a role here, as may other groups of stakeholders coming together to address specific issues. For example, in the area of managing the emergence of resistance to Bt in corn, the USDA NC-205 group (research and extension entomologists of the North Central Regional Research Project) have developed plans for managing resistance to Bt in the European Corn Borer. Such plans involve a monitoring component. Another approach would be to fund the equivalent of the National Science Foundation's Long-Term Ecological Research (LTER) sites. These might be regionally based at Agricultural Experiment Stations and have appropriate outreach to private lands as dictated by monitoring protocols.

As another example, the USDA is setting up regional pest management centers and will work with EPA and APHIS to adapt monitoring needs to regions based on crop/pest/disease complexes.

Pros

--Would allow program flexibility;
--Solicitations for proposals could be issued based on targeted areas;
--Consistent with USDA's plans for regional pest management centers;
--Monitoring activities could be phased in based on the status of the science; and
--Program could grow and shrink based on need or available budget.

Cons

--A voluntary monitoring program would not be viewed as long-term and therefore inadequate to measure possible impacts that might occur over long periods of time – 10 to 50 years out.

- **Mandatory plans**

FIFRA gives EPA the authority to require that registrants provide the Agency information to address identified issues (termed a "data call-in"). In general, EPA uses this authority when the issue applies to a class of pesticides. For example, EPA has called-in data from registrants of pesticides sprayed on crops on the kinetics of drift of sprayed pesticides. The data call-in provisions could be applied to monitoring of genetically engineered plants for specific environmental effects, as appropriate. Similar authorities could be sought for other Federal agencies.

Pros

--Would likely be viewed by environmental groups as a positive step; and
--Would ensure use is tied to specific areas of identified concern.

Cons

--If applied generally, this would be viewed by industry as overly restrictive and costly with little benefit; and
--Would be costly for agencies to enforce.

- **Comprehensive monitoring programs to assess the health of our agro-ecosystems and associated lands and waters.**

This would require significant resources and would raise numerous issues associated with federal/private land use issues. However, if such a program could be established, it would be a powerful management tool for agricultural practice. Ecosystem attributes that could be monitored include: soil erosion; pest, pathogen, and weed populations; biological diversity (genetic diversity); and water quality. The President's Sustainable Development initiative has already made substantial inroads on developing a wide range of environmental indicators that might be useful for monitoring agro-ecosystems.

Pros

--Would provide a useful management tool to monitor the impact of agricultural practices generally; and
--Would likely be supported by environmental groups and others concerned with the overall health of the environment.

Cons

--Would be expensive to implement; and
--Might raise private land use issues if monitoring was conducted on private lands;

PART II: FISH, INSECTS AND MICROORGANISMS

Fish and Shellfish

To remain internationally competitive, the U.S. animal agriculture industry must increase production efficiency, improve quality and safety of food products, and minimize the environmental impact of production. The development of the U.S. aquaculture industry has great potential for immediate and long-term benefit to the nation. Declining natural fishery harvests and rapidly growing populations mean that, worldwide, aquaculture production will need to increase some 300 % by 2025 to meet projected seafood demand. Aquaculture is the fastest growing segment of U.S. agriculture, but domestic aquaculture supplies only about 10% of U.S. seafood needs, and the United States has lagged behind many countries in development of its aquaculture industry (the value of the U.S. aquaculture industry ranks only tenth in the world). The United States imports approximately half of its fishery products, including over $1 billion of foreign aquaculture products, contributing to a multi-billion dollar annual fisheries trade deficit.

Genome research and genetic engineering will be particularly important to the emerging U.S. aquaculture industry. The major research needs and opportunities for aquaculture are not unlike those of other animal agriculture commodities; however, the state of the science is not as advanced. Compared with other animal agriculture species, there has been only limited genetic improvement of aquaculture species, so there is great potential for rapid gains in growth rate, production efficiency, and improved health status of farm-raised fish through targeted genome research. In general, the aquaculture community needs more scientific understanding to bolster the credibility of their attempts to utilize genetically engineered species as well as other management actions.

Research on genome mapping for aquaculture species is conducted at a number of universities, federal agencies such as USDA's Agricultural Research Service, and industry. To date, more then 20 kinds of fish or shellfish have been genetically engineered. Aquaculture species being studied most intensely using federal dollars include catfish, trout, tilapia, oysters, salmon, and marine shrimp. In addition, the NIH supports a large genome project on the experimental model organism zebrafish.

Examples of genetic engineering applications being applied to aquaculture species include: the insertion of growth hormone genes to increase growth rate (one biotech firm claims its salmon can grow 400% faster than non-engineered salmon); insertion of genes to make fish more tolerant to freezing temperatures; and the insertion of anti-microbial genes to resist bacterial infection.

However, with the benefits that might be derived from these genetic modifications come possible risks that must be considered when decisions are being made on whether to place these organisms into the environment and commerce. As with any species introduction into the environment, the ability of a genetically modified aquaculture organism to cause environmental harm needs to be assessed on a case-by-case basis until adequate data exist to make broader generalizations. As stated in a recent paper by Eric Hallerman, et. al., examples of ecological risks include the following:

- the possibility of heightened predation or competition with native organisms;
- colonization by the modified organism in ecosystems outside the native range of the species;
- alteration of population or community dynamics due to activities of the modified organism; and
- interbreeding with natural populations if the engineered species is fertile.

Loss of genetic diversity is already an issue for wild salmon. Attempts to supplement declining wild salmon populations with hatchery-raised fish (non-genetically engineered) are believed to have had many adverse impacts, such as further reducing genetic diversity within and between populations, altered behavior of fish, and displacement of wild runs where hatchery fish have exceeded stream capacity. Genetically engineered salmon released into the wild or that have escaped from aquaculture facilities may exacerbate this problem depending on how fit the modified fish are compared to their wild counterparts.

The existing regulatory framework for aquaculture species is less certain than that for other types of organisms. FDA, under the authority of the Federal Food, Drug, and Cosmetics Act, has clear jurisdiction over food products derived from genetically engineered aquaculture species. FDA is regulating newly inserted genes and gene products as animal drugs and is also addressing environmental concerns. USDA requires scientists to meet a minimum set of requirements before they will fund research that might result in environmental exposures. The Department of Interior authorities would become relevant should the introduction threaten listed or endangered species.

Insects

APHIS has been in the forefront of efforts to facilitate utilization of genetically engineered (transgenic) arthropods while ensuring their safe use. The permit and risk assessment process emphasizes innovation, efficiency, transparency, and customer input. APHIS has also established a clearinghouse for information within the transgenic arthropod research community. The major features of that system involve a web-site (www.aphis.usda.gov/biotech/arthropod) on which all relevant Agency activities are presented. These include screen-readable versions of permit applications, Agency assessment documents, field trial reports, and Agency time-line data. The most recent transgenic arthropod permit, issued in March 1999, involved the pink bollworm, a pest of cotton in Southern California and Arizona. This insect pest was engineered to contain a green fluorescent protein visible under UV light. This genetically engineered organism was to be used in the Sterile Insect Release program to identify lab-reared sterilized insects as opposed to wild-caught insects.

APHIS currently is involved in an effort to ensure safe utilization of Genetically Engineered Arthropod Vectors of Animal Disease (GEAVAD). Presently, the regulations employed by APHIS to ensure animal health and safety do not specifically mention GEAVADs. APHIS therefore has begun the process of developing appropriate regulations and will soon be publishing an Advance Notice of Proposed Rulemaking as a means of soliciting input from the general public and potentially impacted entities. APHIS has already received a permit request to move interstate, between containment facilities, a mosquito vector of animal disease. More applications are expected in the near future, so considerable effort is being expended to develop the appropriate regulations.

When an applicant requests authorization from APHIS under the various plant pest and animal health regulations to import, move interstate, or release into the environment a transgenic arthropod, an assessment process is conducted to determine the potential risks to American agriculture and the environment. This process is conducted in two phases: first, APHIS conducts an examination of the risks associated with the introduction of a nontransgenic form of the proposed species, and second, the Agency examines the potential additional risks associated with the introduction of the transgenic form. When risks are identified, consideration is given to the mechanisms proposed to manage that risk.

Information required from the applicant for a proposed nontransgenic introduction includes data such as the taxonomic identification of the organism, its biology and ecology, the intent of the introduction, its likelihood of success, and the potential impact of the introduction (if a release into the environment) on the target community and ecosystem. When a transgenic arthropod is involved, additional information is required: (1) how the recipient organism was transformed through recombinant DNA technology including characteristics of the donor, vector, and recipient organisms and a description of the methods employed, (2) the characteristics of the modified organism including the stability of the new genotype and the probability of gene transfer to other organisms with resultant consequences, (3) potential impact of the transgenic arthropod on native populations, communities, and ecosystems, and (4) methods for evaluation of the safety of the transgenic organism in field trials before unrestricted release. Efforts are continuing to refine and improve this evaluation process, to upgrade the technical expertise of the associated staff, and to improve communication with the potential regulated community.

Microorganisms

USDA/APHIS and EPA have primary responsibility for overseeing the environmental safety of genetically engineered microorganisms. Primarily under the Plant Pest Act and Plant Quarantine Act, APHIS protects US agriculture from possible harmful effects from genetically engineered microorganisms. Under the Federal Insecticide, Fungicide, and Rodenticide Act, EPA assesses the environmental risks associated with microbial pesticides (e.g., *Bacillus thuringiensis* in a spray formulation). EPA regulates microorganisms, that are not foods, drugs, cosmetics, tobacco, nuclear materials, firearms, under the Toxic Substances Control Act (TSCA). EPA has established under section 5 of TSCA a premanufacture notification review process for "new" microorganisms. Examples of the types of microorganisms subject to TSCA include microorganisms used in the cleanup of toxic wastes (bioremediation), biosensors, and nitrogen-fixing bacteria for natural fertilization of leguminous crops.

Microorganisms play a large number of roles in the environment and may affect other organisms through a number of mechanisms, both direct and indirect. The concern advanced for engineering of microorganisms is a disruption of these interactions.

Pathogenicity. One direct mechanism of interaction is when a proliferating microorganism grows in or on another organism's tissues and directly affects adversely this organism, e.g., a wound becoming infected with *Staphylococcus aureas* or a person contracting tuberculosis. Microorganisms can also have deleterious effects when they produce organic toxins, which can work "from a distance," i.e., the organism producing the toxin grows outside of, at a distance from, the affected organism. For example, humans can be adversely affected by consuming foods containing toxins produced by the bacterium *Clostridium botulinum*. The individual need not ingest the bacterium to be affected.

Various traits have been identified as being possessed by any given pathogenic organism (e.g., the ability to adhere to a cell, the ability to produce a toxin). The concern is that through genetic engineering various traits might be moved from one pathogen to another, or from a pathogen to non-pathogen, resulting in a either a new pathogen or a more aggressive pathogen. The classic example is the acquisition by a pathogen of the ability to resist an antibiotic. Another example is the acquisition by a organism that grows symbiotically in an animal (*E. coli*) of a toxin from a bacterium such as Clostridium. Generally, it is believed that such acquisitions can, and do, occur in nature and are one of the mechanisms by which new, or more aggressive, pathogens emerge. Genetic engineering can be seen as speeding up the evolution of such new or more aggressive pathogens, or as potentially increasing the probability that traits from distantly related organisms might be recombined to create new pathogens (e.g., genetic material from a bacterium spliced into a fungus).

Indirect Effects. There are other less direct ways, in which a microorganism can affect other organisms; for example, by altering a habitat and thereby indirectly affecting populations occupying that habitat. An example of this type of activity is algal blooms in lakes. The bloom produce anoxic conditions (i.e., tie-up all the oxygen in the water), which can lead to disease symptoms and death in oxygen-requiring organisms in the lake (e.g., fish). In this case, the adverse effects are due to anoxia caused indirectly by microbial population imbalances. Indirect affects can also be cause by microbial populations producing inorganic chemicals that can induce abnormal physiological processes in other organisms. For example, microbial populations in sediment can produce enough of an acidic compound (e.g., hydrogen sulfide) that other organisms in the sediment are killed by the acidic conditions. Microorganisms also play a key role in flowrates of environmentally/biologically important substances (e.g., nitrogen, carbon) in mineral cycles. For example, microbial activity is the driving force in carbon cycling in the soil.

The concerns associated with genetic engineering of microorganisms is that the balances among microorganisms, or between microorganisms and other organisms, might be affected by the genetic engineering and result in adverse effects such as those described above.