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Animal and Plant Health Inspection Service

Introduction of Genetically Engineered Organisms

Draft Programmatic Environmental Impact Statement—July 2007

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Background

The Biotechnology Regulatory Services (BRS) program of the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS) regulates the safe introduction (environmental release, interstate movement, and importation) of genetically engineered (GE) organisms. APHIS regulates under the authority of the Plant Protection Act of 2000[1] (PPA), as amended, which combines the authorities of several previous acts, including the Federal Plant Pest Act and the Plant Quarantine Act (PQA). USDA first implemented regulations for GE organisms in 1987, and they have been revised several times[2] to better oversee new technologies and increase APHIS' efficiency.

Under the Coordinated Federal Framework for Regulation of Biotechnology (51 *Federal Register* (FR) 23302), USDA works with the Food and Drug Administration (FDA) and the Environmental Protection Agency (EPA) to ensure that the development and testing of biotechnology products occur in a manner that is safe for plant and animal health, human health, and the environment. USDA and EPA are the agencies responsible for protecting U.S. agriculture and the environment. EPA is responsible for the human/animal health and environmental safety of any pesticidal substance produced in GE plants. FDA is responsible for the safety of the whole food product other than the pesticidal component regulated by EPA.

On January 23, 2004, APHIS published an announcement in the *Federal Register* of its intent to prepare a programmatic environmental impact statement (EIS) to evaluate the environmental impacts arising from alternatives the agency is considering in the revision of its biotechnology regulations. The decision to revise APHIS regulations grew out of interagency discussions, which were led by the Office of Science and Technology Policy and included EPA and FDA. This draft programmatic EIS will thus analyze the environmental impacts on the human environment resulting from APHIS' current regulations for GE organisms as well as to analyze the potential environmental impacts, if any, on the human environment resulting from any revisions or changes to APHIS' current regulations for GE organisms.

[1] The Plant Protection Act of 2000, 7 United States Code (U.S.C.) 7701.

[2] 68 FR 46434 (plant producing industrial compounds); 62 FR 19903 (extensions); 60 FR 43567 (notifications); 58 FR 17044 (notifications and petitions for nonregulated status); 55 FR 53275 (interstate movement of *Arabidopsis*); 53 FR 12910 (interstate movement of micro-organisms).

Purpose and Need

The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) regulates the environmental introduction of genetically engineered (GE) organisms, including crop and noncrop plants, vertebrate and invertebrate animals, and micro-organisms. APHIS regulations are grounded in the most up-to-date science and are designed to provide a level of oversight appropriate for the safe introduction of GE organisms. APHIS is considering whether revisions to its regulations are necessary. One purpose of such revisions would be to address current and future technological trends resulting in GE plants with which the agency is less familiar, such as plants with environmental stress tolerance or enhanced nutrition, and plants engineered for new purposes such as biofuels or for production of pharmaceutical or industrial compounds. Additionally, the regulations would be revised to ensure a high level of environmental protection, to create regulatory processes that are transparent to stakeholders and the public, to consider the efficient use of agency resources, to ensure that the level of oversight is commensurate with the risk, and to ensure conformity with obligations under international treaties and agreements, such as World Trade Organization (WTO) agreements. Any revision of the regulations would be consistent with Executive Order 12866.

In accordance with the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures, APHIS has prepared a draft EIS (DEIS). The purpose of this DEIS is to provide an environmental analysis that compares the impacts of various alternatives to the current regulations. The DEIS will inform the public about the potential environmental impacts resulting from the possible regulatory changes. The DEIS, along with public comments on the document, will provide agency decisionmakers with a full range of alternatives, assist them in selecting a preferred alternative, and help inform the decisionmakers in the rule revision process.

Method

The analysis of the APHIS regulatory program and proposed alternatives includes many issues affecting the current program. During a scoping process, interested stakeholders, government agencies, and the public raised issues that should be addressed in the preparation of the DEIS. Public scoping for this DEIS started January 23, 2004, when APHIS published a Notice of Intent (NOI) in the *Federal Register* to prepare an

EIS and began accepting comments on 11 broad categories of questions posed in the NOI. In addition to gathering written comments during the comment period, APHIS gathered oral comments during meetings with 23 stakeholder groups in February and March 2004, as well as during a meeting with the National Association of State Departments of Agriculture (NASDA) in June 2004. APHIS also sponsored a survey of its members by the National Plant Board (NPB) in regards to biotechnology issues affecting State regulatory officials. The survey results were posted on the NPB Web site[3] in February, 2006.

All comments and proposed alternatives received were evaluated on the basis of whether they addressed the issues in question, whether they were based on valid science, and whether they were reasonable and practicable. The results of the scoping process assisted APHIS in the formulation of the alternatives that are analyzed in this DEIS.

In this document, the various issues and regulatory alternatives are examined by APHIS, the impacts of each alternative are presented, and APHIS' preferred alternative is described. The DEIS examines aspects of the biological, physical, sociocultural, and economic environments that may be affected by APHIS' current biotechnology regulations and the proposed alternatives described in this document. Because it is not possible to compare the impacts of the alternatives under consideration quantitatively, APHIS used qualitative parameters in its analysis.

Current APHIS Regulations

Current APHIS regulations for GE organisms are based on authority in the PPA to regulate the introduction of organisms that may be plant pests or for which there is reason to believe are plant pests. Applicants must submit required information for environmental release, movement, or importation for review by regulatory scientists who evaluate the risks posed by the introduction and the procedures that the applicant will use to minimize those risks. Depending on the nature of the GE organism, an applicant applies for either a permit or a notification. APHIS authorizes introductions after considering the organism, the nature of the genetic engineering, and the ways in which the GE organism is likely to interact with the environment.

A notification is a more streamlined authorization process that is used only for plants with traits considered to be low risk. To qualify for a notification, the GE plant must meet strict eligibility requirements to ensure that it poses a minimal plant pest risk. The GE plant must also be

[3] <http://nationalplantboard.org/docs/2006_brs_review.pdf>

grown under conditions designed to meet performance standards ensuring confinement of the regulated material. The remaining organisms—including plants that are genetically engineered to produce pharmaceutical or industrial compounds—are subject to the permitting process.

Permits are designed to ensure the safe introduction of any GE organism over which APHIS has authority. All required information submitted in a permit application is reviewed by APHIS scientists. Confinement conditions and standard operating procedures are tailored on a case-by-case basis to maintain confinement of the GE organism throughout the course of the introduction. APHIS requires that all plants genetically engineered to produce pharmaceutical or industrial compounds be grown under extremely strict management protocols. These plants are grown in a way that maintains confinement of the plant to the release area, with additional precautions taken to prevent the escape of pollen, seeds, or plant parts from the field test site.

APHIS works to ensure that notification and permit holders maintain regulatory compliance by providing guidance and through procedures that include violation-prevention efforts, site audits and inspections, documentation of compliance infractions, and mitigation and enforcement actions to address any infractions. In addition, APHIS requires the submission of field reports which, in addition to other information, must inform the agency if any adverse effects are noted during any environmental release of GE organisms.

After a GE organism has been field tested extensively and the developer can show that the organism is not a plant pest and can safely be removed from APHIS oversight, the developer may request the deregulation of the organism by filing a petition for a "determination of nonregulated status." After the applicant submits the required data and it has been reviewed by the agency, APHIS prepares an environmental assessment (EA) and if warranted, an EIS to analyze the potential impacts the plant may have on the human environment and seeks public comment as required by NEPA. APHIS approves a petition only when it reaches the conclusion that potential plant pest risks posed by the GE organism are not greater than those posed by similar, non-GE organisms. Once APHIS has deregulated an organism, it may be freely moved and planted without the requirement of permits or other regulatory oversight by APHIS. Deregulated status may be extended to GE organisms which APHIS determines are similar to previously deregulated organisms. Conversely, given new information, APHIS may determine that a previously deregulated GE organism poses a plant pest risk and should, therefore, be brought back under agency oversight.

Alternatives

APHIS developed specific regulatory alternatives to address each of 11[4] issues identified by the agency and elaborated upon through the scoping process. This DEIS compares environmental impacts associated with implementing each alternative. For each issue a "No Action" alternative, in which pertinent regulations are not changed, was also analyzed and considered. Each of the alternatives is analyzed in the DEIS, and a Preferred Action, consisting of a combination of preferred regulatory alternatives, is chosen.

1. Issue 1

APHIS is considering the broadening of its regulatory scope beyond genetically engineered organisms that may pose a plant pest risk to include genetically engineered plants that may pose a noxious weed risk and genetically engineered organisms that may be used as biological control agents. Do regulatory requirements for these organisms need to be established?

Given the rapid advances in biotechnology, the present scope of regulations may not be of sufficient breadth to cover the full range of GE organisms and the full range of potential agricultural and environmental risks posed by these organisms, including risks to public health. Historically, APHIS has used only the authority in the PPA that was originally granted in the Federal Plant Pest Act and the Plant Quarantine Act. Specifically, the agency has used its authority to protect against plant pests as the basis for regulating GE organisms. The PPA, however, redefined authorities and responsibilities for the agency. Changes are now being considered in recognition of these responsibilities and in light of these new technologies.

2. Issue 2

APHIS is considering revisions to the regulations to increase transparency and to address advances in technology that may create new products and concerns. Should a new system of risk based categories be designed to deal with new products and new concern? If so, what criteria should be used to establish the risk-based categories?

Fundamentally, APHIS has always used a risk based approach in regulating GE organisms. However, there is public interest in understanding how APHIS regulates various types of organisms according to risk and familiarity. In addition, there is a trend toward more highly varied organisms and the risk assessment process may need greater flexibility to handle this variety. In recognition of these issues, the agency

[4] Issue 10 in the NOI involved relief of regulatory requirements for low-risk materials. Rather than list regulatory relief alternatives separately, they have been incorporated into the discussion of the other issues, where appropriate.

is considering revising the regulations to make the use of risk-based categories – where GE organisms are classified according to risk and familiarity so that oversight and confinement vary by category – more explicit. Redefined categories may provide added flexibility to better regulate diverse organisms and new types of traits, and provide better clarity to the regulated community and to the public, which may in turn promote greater confidence in the system.

3. Issue 3

APHIS is considering ways to provide regulatory flexibility for future decisions by accommodating commercialization of certain genetically engineered organisms while continuing, in some cases, to regulate the organisms based on minor unresolved risks. Other regulated articles could be treated as they have been under the current system, in which all regulatory restrictions are removed. What environmental factors should be considered in distinguishing between these kinds of decisions?

Once an article has been deregulated, APHIS cannot place any restrictions or requirements on its use, short of re-regulating the article. Restrictions and requirements have not been deemed necessary in the past because BRS risk assessments have concluded that the GE plants APHIS has deregulated pose no greater risks than conventionally bred plants. However, APHIS recognizes that future development and commercialization of plants with less familiar traits may pose new challenges for the agency because even a thorough assessment may not resolve all unknowns regarding an article proposed for deregulation. These unknowns may justify continued scrutiny and data collection or use restrictions, even while allowing planting of the article without a permit. Therefore, APHIS is exploring a system that could give increased flexibility for handling special cases involving less familiar traits by creating provisions that allow for imposition of conditions for unconfined release. This could facilitate commercialization, while requiring appropriate restrictions or monitoring.

4. Issue 4

Are there changes that should be considered relative to environmental review of, and permit conditions for, genetically engineered plants that produce pharmaceutical and industrial compounds?

Genetic engineering technology has advanced to the point where organisms can be developed that produce novel proteins and other substances with biological activity or industrial utility. The gene products made by pharmaceutical and industrial plants may have biological activity or may pose other hazards not associated with proteins and other substances commonly found in the food supply. In practice, any changes

in the confinement of plants producing pharmaceutical and industrial compounds would be based on risk, not solely on the type of plant.

5. Issue 5

The definition of noxious weed in the PPA includes not only plants, but also plant products. Based on that authority, APHIS is considering the regulation of nonviable plant material. Is the regulation of nonviable material appropriate and, if so, in what cases should we regulate?

In some special cases, certain nonviable material originating from a field test (e.g., cell debris, leaves, stems, roots, or seeds) may pose unique types of environmental or human health risks. Currently, APHIS regulates organisms that pose a plant pest risk and does not regulate nonliving material derived from GE organisms. By definition, plant pests are living organisms. However, the noxious weed definition offers an opportunity to regulate nonviable plant products that could "injure or cause damage to crops." Because there may be cases in which potential risks could justify the regulation of nonviable material, APHIS is considering whether it should regulate nonviable material in those cases.

6. Issue 6

APHIS is considering establishing a new mechanism involving APHIS, the States, and the producer for commercial production of plants not intended for food or feed in cases where the producer would prefer to develop and extract pharmaceutical and industrial compounds under confinement conditions with governmental oversight, rather than grant nonregulated status. What should be the characteristics of this mechanism?

For organisms that cannot meet the criteria for deregulation, APHIS is considering whether a new type of permitting system would be more appropriate in terms of efficiency and effectiveness than the current system. In addition, there is much public and State interest in these types of plantings and a new mechanism may increase transparency and allow for greater State involvement.

7. Issue 7

The current regulations have no provision for the low-level presence of regulated articles in commercial crops, food, feed, or seed of GE plant material that has not completed the required regulatory processes.[5] Should low-level occurrence of a regulated article be exempted from regulation?

[5] In the NOI, the term *adventitious presence* was used to refer to the "intermittent low levels of biotechnology-derived genes and gene products occurring in commerce that have not gone through all applicable regulatory reviews." However, APHIS realizes that this term means different things to various interests around the world; hence, we will avoid its use elsewhere in the main body of the EIS.

As with traditional plant breeding, large scale annual field testing of GE plants that have not completed all applicable reviews may result in materials from these trials occasionally being detected at low levels in commercial commodities and seeds. Current regulations do not expressly allow for any such occurrence, though experience continues to show that such occurrences can occur. In a 2002 Office of Science and Technology Policy (OSTP) notice,[6] APHIS committed to conducting a risk-based regulatory program that minimizes the occurrence of these materials and includes safety criteria under which these materials would be allowed at low levels in commercial commodities and seeds.

8. Issue 8

Should APHIS provide expedited review or exemption from review for certain low-risk, imported GE commodities intended for food, feed, or processing that have received all necessary regulatory approvals in their country-of-origin and are not intended for propagation in the United States?

APHIS anticipates an increasing number of requests to import regulated GE organisms that are not intended for propagation, such as organisms that are intended for direct use as food, feed, or for processing. The current regulatory system was designed to handle such requests using permits and notifications. However, in anticipation of this increase, APHIS' goal is to design an efficient system that protects U.S. agriculture and human health without erecting unnecessary trade barriers. To that end, the agency has evaluated several different alternatives.

9. Issue 9

Currently, genetically engineered *Arabidopsis* spp. are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. Should the movement of genetically engineered *Arabidopsis* spp. or other GE organisms be exempted from movement restriction?

Currently, genetically engineered *Arabidopsis* spp. and a few other organisms are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. The agency is considering whether to expand the current exemption from interstate movement restrictions to other well-studied, low-risk, GE research organisms. Such a change would create a consistent, risk based approach to organisms with similar risk profiles.

[6] 67 FR 50577

10. Issue 10

What environmental considerations should be evaluated if APHIS were to move from prescriptive container requirements for shipment of GE organisms to performance-based container requirements, supplemented with guidance on ways to meet the performance standards?

APHIS regulations prescribe the use of several types of packaging to prevent the escape, dissemination, and environmental persistence of GE organisms. Nevertheless, based on APHIS' experience, there are other types of containers that can be used to safely move GE organisms. APHIS often grants applicants a variance to use a different container to transport a GE organism in a way other than prescribed by the regulations; however, reviewing these requests takes agency resources. APHIS is considering alternatives that will reduce the need for variances but still facilitate the safe movement of GE organisms.

The Proposed Action

With respect to the issues and associated alternatives, APHIS has made a preliminary determination that action should be taken, and that the action will require revision of the regulations at 7 Code of Federal Regulations (CFR) part 340. Regulatory revisions under consideration are based on Agency experience and utilize new provisions of the PPA of 2000. They have the potential to increase effectiveness, efficiency, and transparency and decrease negative environmental impacts. They reflect the current thinking and should not be considered as final or as a rule proposal.

APHIS' preliminary determinations are discussed immediately below. For the reader's convenience, each determination as presented is accompanied by a parenthetical reference to its corresponding issue number noted earlier in this Executive Summary.

APHIS has made a preliminary determination that oversight should be increased by expanding the scope of regulations to utilize authorities in the PPA other than just the plant pest provision, specifically, the authority over noxious weeds and biological control organisms (issue 1). The noxious weed provision, in particular, will increase oversight of GE plants by increasing the scope of what is regulated and by allowing a broader consideration of risks. APHIS has also made a preliminary determination to explicitly consider risks to public health in its regulation. Use of this feature would allow APHIS to consider what is known about the potential hazards of the introduced proteins and other substances to humans or animals, if inadvertently consumed or released. This information could, in

turn, be used to impose appropriate regulatory safeguards on introductions of GE organisms.

APHIS has made a preliminary determination to adopt an expanded tiered permitting system based on potential environmental risk and familiarity (issue 2). A detailed example of such a system is described in this DEIS. The goals, with respect to the tiered system, are to increase transparency with respect to how the agency handles various types of GE organisms and also to be highly flexible, such that the agency could move GE organisms among the tiers as new information becomes available. For well characterized low-risk GE organisms, APHIS would continue to use a process similar to the current notification process found in 7 CFR § 340.3; however, a preliminary determination has been made that the term notification should no longer be used. Notification would, for the most part, become the lowest risk "permit" in order to increase transparency and avoid confusion about the status of these organisms as regulated articles.

Other changes under consideration can be integrated easily into a tiered permitting system. For example, the agency has made a preliminary determination to exempt organisms in the tier type representing the most studied and familiar GE organisms from the requirement of a permit for interstate movement (issue 9). Likewise, the policy that the agency is considering for dealing with low level presence of regulated biotechnology materials, when detected in commercial seed and commodities, could be linked to the tiered permitting system (issue 7). APHIS currently thinks the safety criteria for the most familiar and lowest risk permit tier type could also serve as the criteria under which APHIS would not take or order remedial action when regulated materials are detected at low levels in seeds or commodities.

The agency has also made a preliminary determination to adopt a new system in which organisms could be fully deregulated or in which the agency could retain oversight in specific cases as needed (issue 3). It is envisioned that the vast majority of organisms would be fully deregulated and that this determination would be synonymous with deregulation under the current system. The new system could include processes and criteria to allow release and use, with some restrictions, for special cases where there were minor risks that could be mitigated with conditions for safe commercial use.

The Agency has also considered various alternatives with respect to producing pharmaceutical compounds in plants, including whether food crops should be used and whether they should be allowable for open air introductions. APHIS has made a preliminary decision that under highly stringent conditions and with abundant oversight, including a

consideration of food safety, food crops can be safely used for production of these compounds (issue 4). This does not mean that this option would be allowed in all cases. Rather, should APHIS, based on its review of the GE organism and consideration of the potential risks, allow open air testing in appropriate cases.

The agency has made a preliminary determination to create a multi-year permit for GE organisms, with stringent oversight, in cases where developers are not interested or would not qualify for deregulation but plan to produce under permit. This would cover situations where producers are able to commercialize with relatively small plantings (e.g. industrial and pharmaceutical plants) (issue 6). Regulatory rigor would remain high to protect the environment, but efficiency and transparency would increase. The State partnership would be strengthened under this new system. The system would rely on multiyear permits and intensive reviews of standard operating procedures (SOPs), as well as audits and inspections. Though the new system under consideration could be used for pharmaceutical and industrial plants, the agency might also find it appropriate for other types of GE plants.

APHIS has made a preliminary determination that it would be beneficial to regulate nonviable plant material originating from field tests (issue 5) when there is reason to believe, based on scientific review, that such debris might be harmful to the environment if it were allowed to remain. Such an approach could allow the agency to retain oversight if regulations or permit conditions are violated such that nonviable material poses a hazard (e.g., potential food contamination).

APHIS has made a preliminary determination to have a new regulatory mechanism to allow for imports of commodities for nonpropagative use, that is, for food, feed, or processing, in cases where these commodities might not have been deregulated in the United States (issue 8). With this approach, we could establish criteria to ensure safety and allow for additional environmental review when appropriate. Allowing such imports without prior deregulation would not obviate the need to comply with requirements at other agencies, such as FDA and EPA.

This document identifies alternatives which the agency has preliminarily determined would increase regulatory efficiency. These alternatives could be adopted independently of any other alternatives described in the EIS, including any changes in regulatory scope. One provision, mentioned earlier, is to exempt certain GE organisms from the need for a permit prior to interstate movement (issue 9). Another is to allow for a mechanism by which certain classes of GE organisms might be excluded from regulatory oversight after review by the agency (issue 1). This provision would

relieve the need for event-by-event deregulation of that class of organism. The agency also favors moving toward performance-based packaging container requirements as opposed to the prescriptive system which presently exists (issue 10). The agency recognizes that there are numerous types of appropriate containers that can meet a given safety standard.

The environmental impacts of the changes discussed above have been analyzed in the chapter 4.C of this document. The environmental protections provided by these changes would either exceed or be approximately equal to the current system. In some cases, APHIS favors changes because of additional protections. In other cases, a similarly protective regulatory mechanism is favored because it is either more efficient or more transparent than the current mechanism.

Administrative Changes to APHIS Rules

As a part of the revision to 7 CFR part 340, APHIS may also make several administrative changes to its rules in order to improve their clarity, coordination, and execution. No significant environmental impacts from these changes are anticipated.

Public Comment Sought

This DEIS is a comprehensive document designed for more environmentally informed decisionmaking for future regulation of GE organisms under the agency's purview. APHIS now seeks public comments on this DEIS. Following consideration of the comments, APHIS will issue a final EIS in accordance with NEPA. Supplements to the final EIS may be necessary as new or improved processes are developed, changes occur in the program or its administration, or coverage of the document is expanded.

I. Purpose and Need

The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) regulates the environmental introduction of genetically engineered (GE) organisms, including crop and noncrop plants, vertebrate and invertebrate animals, and micro-organisms. APHIS regulations are grounded in the most up-to-date science and are designed to provide a level of oversight appropriate for the safe introduction of GE organisms. APHIS is considering whether revisions to its regulations are necessary. One purpose of such revisions would be to address current and future technological trends resulting in GE plants with which the agency is less familiar, such as plants with environmental stress tolerance or enhanced nutrition, and plants engineered for new purposes such as biofuels or for production of pharmaceutical or industrial compounds. Additionally, the regulations would be revised to ensure a high level of environmental protection, to create regulatory processes that are transparent to stakeholders and the public, to consider the efficient use of agency resources, to ensure that the level of oversight is commensurate with the risk, and to ensure conformity with obligations under international treaties and agreements, such as World Trade Organization (WTO) agreements. To this end, this draft environmental impact statement (DEIS) was prepared to provide agency decisionmakers with a full range of regulatory alternatives and assist them in selecting a preferred alternative.

A. Background

Over the past 2 decades, it has become clear that genetic engineering is a powerful tool for creating improved crop varieties that can be integrated into existing agricultural production systems, and it has the potential to benefit agriculture, the environment, human health, and the U.S. economy. The International Service for the Acquisition of Agri-Biotech Applications has recently reported that GE crops were grown on 222 million acres (or 90 million hectare (ha)) in 2005 by 8.5 million farmers in 21 countries. This marks an 11-percent increase from 200 million acres in 2004. The United States was the largest adopter of GE crops, with 123 million acres planted in 2005.[7] Consistent with the Coordinated Framework for Regulation of Biotechnology (51 *Federal Register* (FR) 23,302 (June 26, 1986)), USDA works with the Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) to make sure that the development and commercialization of GE agricultural products are done safely.

[7] http://www/isaaa.org/kc/

USDA first implemented regulations (7 Code of Federal Regulations (CFR) part 340) for GE organisms in 1987. Under these regulations, plants, micro-organisms, fungi, insects, and mollusks were subject to regulation if they have the potential to pose a plant-pest risk as defined in the regulations. The regulations established a permitting system to authorize importation, interstate movements, and environmental release of GE organisms.

The regulations have been revised several times[8] to accommodate new technologies and to increase APHIS' efficiency. For example, a revision in 1993 introduced the notification option for authorizing introductions. This process was more streamlined than a permit application but originally could be used for only six crops considered by the agency to be low risk and with which the agency was highly familiar. In addition, the genes and transformation methods used had to comply with specific safety criteria that established a very low potential to pose a plant-pest risk.

Another revision in 1993 established a process in which an applicant could petition the agency to determine if a GE plant should be deregulated. In considering a petition, APHIS carefully reviews the data submitted by the applicant, typically amassed during several years of field testing, and also weighs other information, including pertinent scientific studies. APHIS' analyses are grounded in almost 100 years of experience protecting U.S. crops from plant pests, beginning with the enactment of the Plant Quarantine Act (PQA) of 1912. APHIS deregulates a biotechnology-derived plant if the agency finds that the plant poses no plant pest risks to the United States.

In 1997 the regulations were again revised. At that time, the eligibility for the notification procedure was extended to cover all plants with the exception of federally listed noxious weeds and other plants considered by APHIS or a State government to be weeds in the area of the proposed field test. The other eligibility requirements remained the same.

APHIS is again considering whether there is a need to revise its regulations. The need for these considerations and consequently the need for an EIS are being driven by several timely issues, most of which are associated with emerging technologies used to develop the organisms regulated by APHIS. Crop plants bearing genes for insect resistance and herbicide tolerance currently make up the bulk of APHIS-authorized introductions, but there are many genes being studied with which APHIS

[8] 68 FR 46434 (plant producing industrial compounds); 62 FR 19903 (extensions); 60 FR 43567 (notifications); 58 FR 17044 (notifications and petitions for nonregulated status); 55 FR 53275 (interstate movement of *Arabidopsis*); 53 FR 12910 (interstate movement of micro-organisms).

may be less familiar. For example, one new trend is the use of GE plants traditionally used for food and feed as a means to produce not food but compounds for pharmaceutical or industrial use. Another trend is the growing diversity in the types of genes being tested, for example, the enormous number of genes emerging from the rapidly expanding field of plant genomics research.

APHIS anticipates that a growing number of permit applications will be submitted to the agency for the introduction of organisms with traits such as increased nutritional quality, enhanced agronomic performance, improved disease resistance, or the production of novel substances. In addition, many of the GE plants now being field tested were produced without using plant pests or plant-pest genetic sequences. Researchers are also beginning to focus more on perennial plants, such as grasses or trees, which may be capable of establishing and persisting outside the site of introduction. (See table 1–1 for a list of crops and traits that APHIS expects to be developed in the future and possible concerns that have been raised regarding the field testing of those materials.)

Our evaluation of the current program is being driven by a need to respond to emerging trends such as those exemplified in table 1–1, and in the process, the agency will consider opportunities for utilizing the expanded regulatory authority that exists in the Plant Protection Act (PPA) of 2000. In addition, the revisions would address process efficiency to reduce regulatory burdens and make better use of APHIS resources by focusing oversight where it is most needed.

Table 1–1. Types of Crops and Traits in APHIS-Regulated Articles and Possible Issues Raised By Field Testing Them.

Crop or Trait	Issues for Field Testing
Perennial crops	Environmental persistence
Pharmaceutical or industrial compound produced	Inadvertent commingling of potentially toxic materials with food
Stress or disease resistance	Development of invasive weeds
Altered nutritional qualities	Impacts on herbivores
Phytoremediation	Concentration of toxic substances
Insect resistance	Development of resistant insects
Herbicide resistance	Changes in herbicide usage

APHIS also hopes to increase the transparency of its regulatory processes and to engender greater public participation in APHIS decisionmaking. The purpose of this DEIS is to provide a detailed environmental analysis that compares the impacts of the Action alternative (i.e., revising the regulations) with the No Action alternative (i.e., retaining the current

regulations). A decision to revise APHIS regulations may involve many individual changes, and each proposed change will be discussed and analyzed separately, for the sake of clarity.

The EIS will help guide agency decisionmaking in selecting between the alternatives and should also contribute greatly to the transparency of the process by providing ample opportunity for public input and comment on the DEIS and by laying out clearly the rationale for any changes.

B. APHIS Statutory Authority

This section discusses APHIS' general statutory authority to regulate GE organisms as known or potential plant pests.

In 1987, APHIS regulated GE organisms under the authorities of the Federal Plant Pest Act (FPPA)(7 United States Code (U.S.C.) §§ 150aa–150jj, repealed), and the PQA (7 U.S.C. §§ 151–167, repealed) by issuing regulations that effectively classified most GE organisms as plant pests or potential plant pests. The regulations govern the "introduction of organisms and products altered or produced through genetic engineering which are plant pests or which there is reason to believe are plant pests." The introduction of such organisms is prohibited unless APHIS authorizes the introduction.

To date, APHIS has authorized over 15,000 field releases involving GE organisms.[9] Of these, the vast majority involve GE plant species. Less than one percent of the total number of authorized field releases involved nonplant species.

APHIS currently derives its authority to write regulations from provisions of the PPA, which is a part of the larger Agriculture Risk Protection Act of 2000. The PPA (7 U.S.C. § 7701 et seq.) was enacted in June 2000 to consolidate and expand several older laws relating to the regulation of plant pests and diseases, including the FPPA, the PQA, and the Federal Noxious Weed Act (formerly 7 U.S.C. § 2801 et seq.). The PPA was enacted to strengthen and clarify USDA's authority to protect American agriculture against invasion by foreign plants pests and diseases, and the Act specifically provided authority over biocontrol agents. The PPA repealed these old laws but included a savings clause (7 U.S.C. § 7758(c)) which provided that regulations promulgated under them would remain in effect until APHIS issued new regulations under the PPA. APHIS' current regulations are, therefore, based on its authority to regulate plant pests originally granted in the FPPA and PQA.

[9] http://www.isb.vt.edu/cfdocs/foe;dtests1.cfm

The PPA provides APHIS with broader authority to regulate GE organisms than the previous statutes. The PPA confers very broad authority on the Secretary of Agriculture to prevent the dissemination of plant pests, noxious weeds, and biological control organisms into or within the United States.

In the PPA, Congress recognized that—

> "…the unregulated movement of plant pests, noxious weeds, plants, certain biological control organisms, plant products, and articles capable of harboring plant pests or noxious weeds could present an unacceptable risk of introducing or spreading plant pests or noxious weeds (7U.S.C. §7701(7))."

Congress charged the Secretary of Agriculture with the task of facilitating exports, imports, and interstate commerce in agricultural products, "in ways that will reduce, to the extent practicable, as determined by the Secretary, the risk of dissemination of plant pests or noxious weeds" (7 U.S.C. § 7701(3)).

Under the PPA, APHIS is responsible for preventing the importation and interstate dissemination of plant pests and noxious weeds. The PPA authorizes APHIS to regulate, "any plant, plant product, biological control organism, noxious weed, article, or means of conveyance" that could spread a plant pest or noxious weed (§ 7712). The definition of "plant pest" in the PPA is broad and includes living organisms that could injure, damage, or cause disease in any plant or plant product (§ 7702(14)). The definition of "noxious weed" in the PPA is arguably even broader than the definition of plant pest; it includes—

> "…any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment. (7702(10))."

The PPA also granted broad authority over biological control organisms, defined as, "any enemy, antagonist, or competitor used to control a plant pest or noxious weed" (7 U.S.C. § 7702(2)).

APHIS regulates potential plant pests and potential noxious weeds both those that are naturally occurring and those that are genetically engineered. APHIS' regulations in 7 CFR § 330.200 are applicable to

persons seeking to import or move interstate, plant pests and noxious weeds that are naturally occurring and have not resulted from genetic engineering. Regulations in 7 CFR part 340 apply to introductions of GE organisms but apply only to GE organisms that are plant pests or potential plant pests: APHIS does not currently regulate GE organisms as potential noxious weeds. Under current regulations, APHIS treats regulated GE organisms similarly to naturally occurring plant pests or potential plant pests. In both cases, a permit must be obtained from APHIS prior to importation, interstate movement, or environmental release, for example, field testing.

C. Interrelationships with Other Federal Agencies

Under the current system of regulating plant pests and potential plant pests, APHIS has broad jurisdiction over GE organisms that have been developed for release into the environment. Two other agencies also have regulatory authority over many GE organisms. Through a registration process that is independent of APHIS, EPA regulates the sale, distribution, and use of pesticides in order to protect health and the environment. This includes pesticides that are produced by organisms developed using techniques of modern biotechnology.

Under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), the Biopesticides and Pollution Prevention Division of the Office of Pesticide Programs regulates the distribution, sale, use and testing of pesticidal substances produced in plants and microbes as well as the microbes themselves if EPA considers them to be biocontrol agents or pesticidal in function. Under FIFRA, EPA also regulates the herbicides that are applied to GE herbicide-tolerant crops, and under the Federal Food, Drug, and Cosmetic Act (FFDCA), EPA regulates pesticide residues. Additionally, under section 5 of the Toxic Substances Control Act (TSCA), EPA acquires information in order to identify and regulate potential hazards and exposures of all new chemicals intended for entry into commerce that are not specifically covered by other regulatory authorities, for example, substances other than food, drugs, cosmetics, and pesticides. TSCA's applicability to the regulation of products of biotechnology is based on the interpretation that micro-organisms are chemical substances under TSCA.

FDA is responsible for ensuring the safety and proper labeling of all plant-derived foods and feeds, including those developed through genetic engineering. All foods and feeds, whether imported or domestic and whether derived from plants modified by conventional breeding techniques or by genetic engineering techniques, must meet the same

rigorous safety standards. Under the FFDCA, it is the responsibility of food and feed manufacturers to ensure that the products they market are safe and properly labeled. In addition, any food additive, including ones introduced into food or feed by way of plant breeding, must receive FDA approval before marketing. To help sponsors of foods and feeds derived from GE plants comply with their obligations, FDA encourages them to participate in its voluntary consultation process. In that process, sponsors provide to FDA data and information that summarizes the basis on which the sponsors have concluded that a GE food is as safe as comparable non-GE food in the food supply. FDA believes that developers of bioengineered food that is intended to be commercially marketed have followed the recommendations in FDA's guidance documents for consulting with FDA.

APHIS has consulted with and requested both agencies' input during the preparation of this DEIS. Both agencies have provided their comments to APHIS, and APHIS now invites both agencies to comment on this published draft. It is APHIS' intention that the alternatives analyzed in this DEIS will be consistent with the Coordinated Framework and will be compatible with the authorities of EPA and FDA. This DEIS will not affect the authorities of EPA, FDA, or any other agency, nor is it APHIS' intention for the proposed revision process to have any such effects. The proposed revision process will not force EPA, FDA, or any other agency to revise its regulations.

D. Biotechnology Regulatory Services Regulatory System

Companies and organizations that wish to introduce a regulated GE organism into the United States must obtain APHIS permission if that organism is a plant pest or is believed to be a plant pest. Applicants must submit all plans for interstate movement, importation, or environmental release for review by regulatory scientists, who evaluate the procedures that the applicant will use to ensure that the GE organism will not escape into the environment or persist there. Depending on the nature of the GE organism, an applicant files either a notification or a permit application. APHIS evaluates the application to determine whether the proposed testing or movement conditions are adequate to confine the GE organism. Biotechnology Regulatory Services (BRS) of USDA–APHIS also works closely with States to be sure that they are aware of environmental releases taking place within their jurisdiction, to explain how the releases are performed and confined, and to allow them to request any additional conditions in accordance with the PPA. To ensure compliance with the

permitting conditions, BRS inspects release sites and audits records maintained by permit holders.

1. The Notification Process

Currently, most regulated GE plants are introduced (i.e., imported, moved interstate, or released into the environment) under "notification," which is a streamlined review process. Applicants may use the notification process only for plants with traits that BRS considers to have little potential to pose plant-pest risks and with which the agency is highly familiar. Examples of plants introduced under the notification process are those altered to induce insect resistance or herbicide tolerance.

To qualify for the notification process, the GE plant must meet six requirements to ensure that it does not pose a potential plant-pest risk:

1. The plant species must be a species that APHIS has determined may be safely introduced; it may not be a plant recognized by APHIS as a noxious weed; nor can it be a noxious weed in the area where any field testing is proposed.

2. The introduced genetic material must be stably integrated.

3. The function of the introduced genetic material must be known and its expression in the regulated article does not result in plant disease.

4. The introduced genetic material does not produce an infectious entity, toxicants to nontarget organisms likely to feed or live on that plant species, or products intended for pharmaceutical or industrial use.

5. The introduced genetic sequences derived from plant viruses do not pose a significant risk of the creation of any new plant virus; and

6. The plant has not been modified to contain certain genetic material derived from an animal or human pathogen (7 CFR § 340.3(b)).

Applicants must also agree to adhere to performance standards set forth by APHIS for proper confinement of the GE plants. The goal of proper confinement is to ensure that the GE plants do not persist in the environment. APHIS requires that applicants provide detailed information about the plant (e.g., the source and identity of any genes introduced, the method of genetic engineering, and the size, duration, and location of the field release). If a plant does not meet the criteria for notification, the applicant must obtain a permit (7 CFR § 340.4) in order to introduce the organism.

When APHIS receives a notification application, it is reviewed by a staff biotechnologist to verify that the application is complete and that the GE plant proposed for introduction meets the criteria for a notification. If BRS completes the review process and finds that all regulatory requirements have been met, the notification is authorized in a process termed "acknowledgement," and the applicant is free to proceed with the proposed introduction under the terms of the notification after the acknowledgement. BRS' acknowledgement of a notification usually applies for 1 year from the date of introduction (7 CFR § 340.3(e)(4)).

2. The Permit Process

The permit process is for GE plants that cannot be introduced under notification—such as plants that produce pharmaceutical or industrial compounds—and for any nonplant GE organisms covered in the regulatory definition of "plant pest." Conditions imposed on field releases performed under a permit are typically more restrictive than those imposed on releases done under notifications, and according to APHIS regulations, the applications may take up to 120 days to process. Applicants must also apply for permits for the interstate movement or importation of a regulated article, which take up to 60 days to process. Upon approval, permits are generally valid for 1 year from the date of issue and are renewable.

For an environmental release, permit applicants must provide APHIS with details about all introduced genetic material and gene products, the biology of the organism, its origin, its intended use, and procedures for field production and isolation. For movement or importation permits, applicants must also disclose the destination, the means of movement, and procedures to safeguard against the escape of the GE organism. For the importation of a GE organism, an applicant must submit an application for each individual shipment. Using the information supplied by the applicant, APHIS scientists create a set of permit conditions with which the applicant must comply or face potential enforcement action. Although there are some conditions common to most permits for GE plants (e.g., sound agronomic practices), permit conditions for nonplant GE organisms are developed on a case-by-case basis.

Applicants may also request nonrenewable, "comprehensive" permits, under which multiple phenotypes, genes, and donors, and all anticipated field test sites and movements for a single crop are included in a single application. Very few applications for comprehensive permits are received.

APHIS forwards the applications for all permits and notifications, with any confidential business information (CBI) redacted, to State regulators in the States to which regulated articles will be moved or in which a field release is planned. This is done to notify States of the requested action

and to allow States to review and comment on proposed releases, importations, or movements. The response from individual States varies: some agree to the proposed introduction under the conditions imposed by APHIS while others request additional permit conditions. For various reasons (e.g., lack of resources), some States choose not to respond.

Most permits and notifications are done under a categorical exclusion under APHIS' NEPA implementation regulations; however, if a permit application or notification involves new species or new organisms or novel modifications that raise new issues, APHIS will prepare an environmental assessment (EA) in compliance with the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures. In the EA, APHIS assesses the potential for the proposed introduction to cause significant impacts to the human environment. APHIS makes draft EAs available to the public for comment, responds to these comments, and publishes a final EA before it determines whether the permit will be granted. If APHIS determines in the EA process that the proposed introduction of a GE organism will cause significant impacts to the human environment, NEPA requires that an EIS be prepared prior to deciding whether to allow the introduction to proceed.

3. Petition for Deregulation

Developers of new GE organisms can petition APHIS for a "determination of nonregulated status." In the petition, a company or organization must submit data to demonstrate that the organism poses no greater plant-pest risk than the non-GE version of the organism. The necessary data includes, at a minimum, a description of the biology of the organism before it was genetically engineered; differences between the GE organism and the original organism; and field reports for all releases the petitioner conducted involving the GE organism. Depending on the organism and the GE trait involved, the petitioner may also need to consult with EPA or FDA. To date, GE plants are the only GE organisms that have been deregulated through the petition process.

Before a GE organism can be deregulated, APHIS prepares an EA or an EIS, in compliance with NEPA, to analyze the impacts the organism may have on the human environment. This assessment includes an examination of potential impacts on plant and animal life and specifically looks for possible impacts on threatened and endangered species (TES), using an ESA assessment which asks specific questions regarding the likelihood that the deregulation of a GE plant would impact TES or critical habitat. APHIS' TES analysis takes into account the likelihood that a deregulated GE plant may be adopted and grown throughout the United States. APHIS publishes in the *Federal Register* all EAs and EISs it

develops and seeks public comment, in compliance with the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures. APHIS approves petitions only when it reaches the conclusion that potential plant-pest risks are no greater than those posed by appropriate non-GE comparator organisms. Petitioners are notified within 180 days after receipt of their completed petition that it has either been granted or denied. According to the regulations, APHIS may approve a petition "in whole or in part." However, to date, no petitioner has requested, nor has APHIS granted, partial approval of a petition for nonregulated status.

Since 1987, APHIS has overseen the deregulation of more than 70 GE organisms, all of which are plants. Of these approved organisms, approximately 40 percent were engineered for herbicide tolerance and approximately 25 percent for insect resistance. Corn, tomatoes, and cotton are the most frequently deregulated organism. (See <http://www.aphis.usda.gov/brs/not_reg.html>.) Each deregulation to date covers not only the original transformed genotypes described in the petition but all progeny that may be subsequently created from the original genotypes. If APHIS becomes aware of information that indicates that a deregulated article poses a plant pest risk, it can be re-regulated by the agency.

4. Extension Requests

If an applicant wishes to seek nonregulated status for a GE organism that is similar to one already deregulated by the agency, the applicant may file an extension request. The agency reviews data submitted by the applicant and then determines if the new organism is in fact the same as the previously deregulated organism with respect to risks. If so, the agency can extend the nonregulated status to cover the new organism. Also, APHIS can, in the absence of an applicant's request, independently determine that a particular organism is sufficiently similar to a previously deregulated organism such that it can be granted nonregulated status**.**

5. Compliance with BRS Regulations

It is the responsibility of APHIS to establish and enforce regulations that protect American agriculture, the food supply, and the environment while allowing for the safe field testing, importation, and movement of GE organisms. APHIS determines the conditions under which GE organisms can be introduced into the United States and allows their introduction only after all necessary safeguards are put into place. Failure to adhere to APHIS regulations and all permit conditions can result in serious penalties, which can be up to $500,000 for all violations adjudicated in a single proceeding. In addition violators may be held responsible for any necessary remediation.

APHIS–BRS' compliance unit works to ensure that notification and permit holders maintain regulatory compliance by providing guidance and through procedures that include violation-prevention efforts, site audits and inspections, documentation of compliance infractions, and mitigation and enforcement actions to address any infractions. In addition, researchers are required to inform APHIS if any adverse effects are noted during the field testing of GE organisms. Compliance specialists and APHIS inspectors perform both targeted and random inspections and audits of field releases to thoroughly monitor potential compliance problems.

E. Scoping

The analysis of the current APHIS–BRS regulatory program and proposed alternatives cover many issues affecting the current program. Such issues were identified in a scoping process during which interested stakeholders, government agencies, and the public raised issues that should be addressed in the preparation of the final EIS. Public scoping is required under the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures. Scoping for this DEIS began on January 23, 2004, when APHIS gave notice in the *Federal Register* (69 FR 3271) of its intent to prepare a DEIS. The notice listed a range of issues to be discussed in the EIS:

1. Should APHIS continue to regulate GE organisms solely on the basis of potential risks as plant pests, or should they also be regulated based on other potential risks such as those for noxious weeds and biological control organisms?

2. Should a new system of risk-based permit categories be designed to deal with new products and new concerns?

3. Should APHIS continue to accommodate commercialization but in some cases grant conditional approvals when additional information is needed about particular regulated articles proposed for deregulation?

4. Should APHIS modify its rules for regulating and confining plants producing pharmaceutical and industrial compounds?

5. Should APHIS regulate nonviable plant material derived from regulated plants?

6. Should there be a new mechanism to provide oversight for pharmaceutical plants and other GE plants that are being produced commercially?

7. Should low-level occurrence of a regulated article be exempted from regulation?

8. Should low-risk organisms intended for importation for a nonpropagative use be exempted from regulatory review or be subject to expedited review?

9. Should interstate movement of GE *Arabidopsis* or other GE organisms be exempted from movement restrictions?

10. Should APHIS consider relieving other regulatory requirements when the environmental risk is low?

11. Should APHIS switch from prescriptive packaging-container requirements to performance-based ones?

The notice solicited public involvement in the form of written comments regarding the above issues and alternatives for regulatory revision. Written comments were accepted from the public during an extended comment period which lasted until April 13, 2004. (See <http://www.aphis.usda.gov/brs/eis/eis_comments.html> and appendix C.)

Oral comments were received from stakeholders (the regulated community, nongovernmental organizations, and university faculty) during meetings with APHIS staff, occurring late February and early March 2004. Twenty-three groups participated in the comment process, and all comments were transcribed and have been made available on the APHIS Web site. (See <http://www.aphis.usda.gov/brs/stakeholder_minutes.html> and appendix D.) In addition, APHIS–BRS sponsored a 3-day conference and workshop with the National Association of State Departments of Agriculture (NASDA) in June 2004. During this meeting, State agriculture personnel were able to voice their concerns and suggestions for APHIS' rule revision process. (See appendix E for a summary of the results of the NASDA discussions.)

F. Scoping Analysis and Documentation

All comments and proposed alternatives received were evaluated on the basis of whether they addressed the issues in question, whether they were

based on valid science, and whether they were reasonable and practicable. The results of the scoping process assisted APHIS–BRS in the formulation of the alternatives that are analyzed in this DEIS. Relevant issues raised through the scoping process were incorporated into the formulation of the regulatory alternatives as described in chapter 2.

A summary of the public comments, those of the stakeholder sessions, and those of NASDA representatives are provided in appendix C, D, and E respectively. For the sake of transparency, the actual text of all public comments and the transcripts from the stakeholder sessions have been published on the APHIS Web site.

G. Requirements for Further Environmental Analysis

This DEIS is a programmatic document that analyzes the environmental impacts of an entire regulatory program. As such, the DEIS addresses these impacts at a general level because of the broad area over which these impacts might occur. Project-specific NEPA analyses and documentation on proposed actions, such as permit applications and deregulation decisions, may be prepared on individual project levels, and public involvement will be solicited in accordance with the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures. These NEPA analyses will be tiered to this DEIS and other applicable EISs where appropriate.

APHIS will issue a final programmatic EIS that addresses public comments received on this DEIS, in accordance with NEPA. Supplements to the final programmatic EIS may be necessary as new or improved processes are developed, changes occur in the program or its administration, or coverage of the document is expanded. Two classes of supplements will be produced:

- Insignificant Supplements: Supplements that cause no substantive change in emphasis or classes of activities and do not have significant environmental impacts (40 CFR § 1508.27).

- Significant Supplements: Supplements that substantively change program emphasis or that have potentially "significant" impacts to the environment (40 CFR § 1508.27).

Insignificant supplements will be made by the APHIS Administrator or his or her delegated representative with appropriate public notification.

Significant supplements will be subjected to NEPA analysis and put in force with the appropriate NEPA documentation and determination as required by CEQ and APHIS NEPA implementing regulations.

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II. Proposed Program Alternatives

Genetic engineering refers to the process in which genes or other genetic elements from one or more organisms are inserted into the genetic material of a second organism using molecular biology methods. Moving a new gene or genes in this way allows researchers to introduce useful new traits into an organism from individuals of the same species or from unrelated species.

The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS) is responsible for regulating the introduction (importation, interstate movement, and environmental release) of genetically engineered (GE) organisms that are known to, or could, pose a plant-pest risk. GE organisms are considered to have the potential to pose a plant-pest risk if the donor organism, recipient organism, vector, or vector agent used in their creation is a member of a genus (listed in the regulations at 7 Code of Federal Regulations (CFR) part 340) known to contain plant pests.

APHIS established Biotechnology Regulatory Services (BRS) in August 2002, by combining units within the agency that dealt with various aspects of the regulation of biotechnology. APHIS exercises its authority through regulations (7 CFR part 340) promulgated under the Plant Pest Act (FPPA). APHIS has regulated biotechnology since 1987, ensuring the safety of 15,000 authorized field releases.

A. Biotechnology Regulatory Services' Goals

BRS' goal is to protect America's agricultural and natural resources by ensuring the safe development of GE organisms using a risk-based regulatory framework, grounded in science. In the implementation of our mission and vision, BRS has established five guiding principles, consistent with Executive Order 12866, that set program direction and provide the foundation for decisionmaking:

1. Rigorous, thorough, and appropriate regulation supported by strong compliance and enforcement.

2. Transparency of the regulatory process and regulatory decisionmaking.

3. A science-based system in place to ensure sound decisionmaking and assure safety.

4. Communication, coordination, and collaboration with the full range of stakeholders.

5. International leadership in capacity building for science-based policy and standards.

How the Draft Environmental Impact Statement Was Developed

APHIS has more than 19 years of experience safely regulating the introduction of GE organisms, operating under the five guiding principles listed above. To ensure that these regulatory goals can continue to be met, APHIS decided to undertake an evaluation of potential revisions to APHIS' regulations to address changes that have occurred in the field of agricultural biotechnology since the agency's regulations were first published in 1987.

On January 23, 2004, APHIS published in the *Federal Register* a Notice of Intent (NOI) to prepare a programmatic environmental impact statement (EIS), in compliance with the National Environmental Policy Act (NEPA) and APHIS' own NEPA implementation rules. The NOI posed several questions in broad categories related to issues that could be of concern. The 60-day comment period closed on March 23, 2004, but was extended on March 26 for another 15 days, closing on April 13, 2004. Approximately 4,000 public comments were received and reviewed by APHIS. Approximately 3,600 of these comments were form letters that expressed general opposition to GE organisms with particular concern being directed at plants genetically engineered to produce pharmaceutical compounds. These and all other comments were analyzed, and APHIS collected all unique issues.

In February and March 2004, the agency held meetings with numerous stakeholders—including biotechnology crop manufacturers, university researchers, food milling and processing organizations, and public-interest citizens' groups. In June 2004, APHIS met with representatives from State departments of agriculture to get their perspective on its regulatory program for biotechnology.

APHIS used all the comments that it collected from the *Federal Register* notice and various meetings in scoping the draft EIS (DEIS) to ensure that the agency was addressing all pertinent issues and that the EIS examined appropriate environmental impacts that could possibly result from revisions to the regulations. The results of the scoping process are summarized throughout this chapter in the context of the major issues discussed in the NOI.

Next, APHIS developed alternatives, that is, specific actions that might be taken to address each of the issues identified by the agency. These alternatives were then elaborated through the scoping process. The alternatives were independent of each other but not mutually exclusive: the alternative chosen to address one particular issue would not necessarily dictate which alternative would need to be chosen to address a different issue. In several cases, more than one alternative could be adopted to address a single issue. For each issue, APHIS articulated a "No Action" alternative, which means the pertinent regulations would not be changed. When appropriate, alternatives incorporated suggestions derived from the public scoping process.

B. Issues and Alternatives

In this section below, each of the issues,[10] is restated along with a list of possible alternatives for action.

1. Issue 1

APHIS is considering the broadening of its regulatory scope beyond genetically engineered organisms that may pose a plant pest risk to include genetically engineered plants that may pose a noxious weed risk and genetically engineered organisms that may be used as biological control agents. Do regulatory requirements for these organisms need to be established?

Given the rapid advances in biotechnology, the present scope of regulations may not be of sufficient breadth to cover the full range of GE organisms and the full range of potential agricultural and environmental risks posed by these organisms, including risks to public health. Historically, APHIS has used only the authority in the PPA of 2000 that was originally granted in the FPPA and the PQA. Specifically, the agency has used its authority to protect against plant pests as the basis for regulating GE organisms. The PPA, however, redefined authorities and responsibilities for the agency. Changes are now being considered in recognition of these responsibilities and in light of these new technologies.

Alternatives Relating to the Scope of Regulations

Consideration of Noxious Weed Risks

Certain organisms that can cause harm or injury to plants or plant products are defined by the PPA as "plant pests" (7 United States Code (U.S.C.)

[10] Issue 10 in the NOI involved relief of regulatory requirements for low-risk materials. Rather than list regulatory relief alternatives separately, they have been incorporated into the discussion of the other issues, where appropriate.

7702(14)). APHIS has used its authority to regulate the introduction and movement of plant pests as the basis for its regulation of GE organisms. Specifically, APHIS regarded any GE organism as a regulated article if the donor organism, recipient organism, vector, or vector agent used to alter or produce the organism is a plant pest. In addition, APHIS asserted its authority if there was a reason to believe the organism could pose a plant-pest risk. The "reason to believe" clause has generally been interpreted to mean that APHIS has ultimate discretion in determining whether a given organism has the potential to pose a plant-pest risk. As a matter of practice, the agency has used this discretion any time there was uncertainty with respect to an organism's plant-pest potential. Because most GE plants use sequences from plant pests, and because the reason-to-believe clause broadens the scope of agency discretion, APHIS believes that its current regulations provide very broad jurisdiction over GE plants.

The question has arisen whether a GE organism that does not present a potential plant-pest risk might pose other potential risks that are addressed by the PPA. One of the reasons for this question is the growing use of gene regulatory sequences from sources other than plant pests, whereas in the past, most gene regulatory sequences were from plant viruses or plant-pathogenic bacteria. A report by the National Academy of Sciences' National Research Council (NRC), entitled *Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation* (NRC, 2002), suggested that USDA should clarify the scope of its coverage. In NRC's opinion, some GE plants not automatically meeting the regulatory definition of a plant pest "lead to instances where public health or environmental issues might not be adequately addressed." The NRC also argued that USDA should regulate all transgenic plants, as there is no scientific basis on which to forecast which ones might pose a risk.

Recently, new types of traits have been engineered, such as GE plants that produce proteins and other substances for use in pharmaceutical or industrial products. These types of traits would not be likely to confer a plant-pest risk to the plants but may pose other types of risks (e.g., health risks to humans) or environmental risks (e.g., toxicity to animals) that may not involve injury to plants or plant products. APHIS does not currently regulate GE plants or other organisms on the basis of their potential to pose these types of risks.

Therefore, APHIS is exploring the use of other authorities, in addition to its plant-pest authority, that might be appropriate to regulate GE organisms. Specifically, the PPA authorizes the regulation of "noxious weeds," which are defined as:

> "…any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or

> plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment. 7 U.S.C. 7702(10)."

Proposing to regulate under the "noxious weed" provisions of the PPA would not mean that APHIS has determined that all GE plants are noxious weeds. However, APHIS has reason to believe it is possible for a plant to be genetically engineered with genes that might give the plant the characteristics of a noxious weed, and APHIS wants the ability to ask not only whether a GE organism is a plant pest, but also whether a GE plant may be considered a noxious weed.

There are many instances in which the noxious weed authority would allow APHIS to assess risks beyond plant pest risks. Many developers are combining multiple GE traits in a single plant variety, and these gene combinations may have noxious weed effects but no plant pest effects. For example, a plant could be genetically engineered with genes to increase its fitness to the point where the plant could become invasive in the wild. This situation could be exacerbated if the plant had weedy wild relatives. Alternatively, a plant could be engineered to produce a substance with the potential to be toxic, allergenic, or otherwise biologically active in humans, and its unconfined release could pose risks to public health. Some plants engineered to produce pharmaceutical or industrial compounds might be examples. GE plants may also be developed with transgenes of unknown function, and it would be important for APHIS to be able to look at the broadest range of possible impacts resulting from releasing the plant in the environment.

The use of this authority could, therefore, provide APHIS with additional information to ascertain whether the introduction of any GE plant intended for use in the environment could result in agricultural or environmental harm. Of particular interest is that, using the noxious weed provision, APHIS would have authority to consider public health effects of GE plants. This could be used to consider the safety of a new protein or other substances both in setting conditions for environmental release and in the decision to deregulate. APHIS might require that questions of food safety be addressed before deregulating a GE plant.

One active area of research is in the use of genetic engineering to produce and enhance biological control organisms, which are defined in the PPA as, "any enemy, antagonist, or competitor used to control a plant pest or noxious weed" (7 U.S.C. 7702(2)). At present, such organisms would be regulated as GE organisms by APHIS only if they also fit the plant-pest criteria used in the definition of a regulated article. However there is

concern that all genetically engineered biological control organisms should be evaluated, using the broader authority in the PPA, until it has been determined that they do not pose risks to agriculture and the environment. The rationale is that many biological control organisms used to date have themselves been plant pests, or if not, they are used in such a way that they interact directly with plant pests or noxious weeds in order to exert their intended effect. Thus, it is appropriate to evaluate genetically engineered biological control organisms to ensure that they do not pose a direct or indirect plant pest or noxious weed risk. These changes should enhance the agency's ability to prevent the dissemination of plant pests and noxious weeds by expanding the scope to include some organisms that might pose such risks, but that are not expressly covered in our current regulations.

Event-based Versus Trait-based Regulation

Currently, APHIS regulates GE organisms as "transformation events." An event is a single successful insertion of a gene or gene fragment into a cell's genetic material or a successful deletion of a gene or gene fragment from a cell. Each event can be genetically unique, even if the event results from a single transformation experiment in which many individual cells were treated under identical conditions. Biotechnology techniques allow scientists to regenerate entire organisms, such as whole plants, from a single cell. A plant produced from one transformed cell may also be called an event.

Typically, APHIS receives field test applications from researchers who wish to test a population of genetically identical plants resulting from a single transformation event. Each transformation event is given individual consideration by APHIS biotechnologists for introductions authorized under notifications and permits and when a petition for determination of nonregulated status is received. This approach is compatible with a definition of a regulated article that includes the noxious weed and biological control organism provisions as well as potential plant pest risk. One alternative is to continue to regulate on an event-by-event basis, but to utilize new provisions in the PPA, specifically those for noxious weeds and biological control agents as described above.

Although the NRC has stated that an event-by-event approach, that is, using genetic transformation alone, is a practical and useful trigger for regulation, the NRC has consistently stated that once a GE organism is deemed subject to regulation, the focus should be on the assessment of the phenotype of the GE organism which results from the genetic engineering process (NRC, 1989; NRC, 2000; NRC, 2002). An alternative approach to event-by-event regulation would be a trait-based approach. GE plants

would be regulated based on the engineered genes in the plant (the genotype) and the traits resulting from those genes (the phenotype), particularly traits that cannot be expressed by an organism through any means other than genetic engineering. Such traits are functionally unknown in the organism and may have ecosystem-level effects and effects on the fitness of the organism that are also unknown. This is of special concern for organisms that have wild or feral, sexually compatible relatives in the environment (Strauss, 2003). An important difference in this approach as compared to APHIS' current system is that once an organism of a particular phenotype was deregulated, plants produced subsequently using genetic engineering that have the same transgene and phenotype would be considered familiar, and, therefore, they would not trigger regulation.

If a trait-based alternative were adopted, APHIS would still need to rely on one or more provisions in the PPA, regulating each novel phenotype and assessing whether it created the potential for the GE organism to be a plant pest or noxious weed. From a regulatory standpoint, APHIS could elect to concentrate its resources on those organisms developed through genetic engineering that exhibit novel phenotypes, that is, phenotypes unknown within the species or within sexually compatible relatives and exclude from regulation those organisms that have a familiar phenotype. Questions regarding familiarity are based on available scientific data, such as data published in scientific journals, data developed by permit applicants, and information collected by the agency itself.

APHIS would then focus on plant phenotypes with which there is little or no experience in the plant-breeding, agronomic, or ecological communities. Organisms exhibiting phenotypes not possible to generate through any means other than genetic engineering would be considered regulated articles. However, APHIS recognizes that the agency may, over time, gain familiarity even with completely novel traits, for example, a trait for environmental stress tolerance that enabled the plant to thrive outside the normal range of the parent plant or its relatives.

Excluding Certain Organisms Based on Risk

The agency is considering whether organisms should be excluded from regulatory oversight after it is demonstrated that they pose no risk or which are adequately regulated by another Federal agency. It has been suggested that existing scientific data be used to identify GE organisms that require little or no oversight based on the plant–trait combination (Hancock, 2003). The specifics of how the exclusion mechanism would work could be either an administrative action, analogous to a deregulation under the current system, or a rule-making mechanism that would be

followed for all excluded organisms or classes. If deregulation or some synonymous mechanism were to be used as the exclusion mechanism, it would be applied to classes of organisms, not individual events.

The agency may wish to use such a mechanism to exclude certain types of organisms that APHIS deems safe based on an extensive history of safe use (e.g., the *nptII* gene). GE organisms that are regulated effectively by other agencies (e.g., a GE biological control organism regulated by the Environmental Protection Agency (EPA) under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)) might be excluded as well.

Another example of a GE organism which might be considered for exclusion would be one in which DNA used to develop a GE plant was derived from the same species or a sexually compatible species (intrageneric). Highly domesticated plant species with no wild or weedy relatives that have been genetically engineered with intrageneric DNA would be expected to pose environmental impacts comparable to the same plants modified via conventional breeding (Strauss, 2003). Conventional plant breeding is considered to be a safe process with few significant environmental impacts, except for a few isolated cases (NRC, 1989; 2000). More importantly, agricultural science has experience in managing the type of risks that may rarely occur. For well over 100 years, plants have been modified using classical and other breeding techniques for the safe development of new varieties that have been evaluated through standardized, structured variety trials. Plant breeders have many established protocols for handling and eliminating undesirable phenotypes produced as a byproduct of creation of genetic variation, and these protocols are applied when any type of plant is used in breeding programs, including GE plants. Therefore, for plants genetically engineered using intrageneric DNA, the risks appear no greater than for plants produced via conventional breeding, which are not subject to Federal regulation.

A mechanism to exclude certain organisms from regulatory oversight could be used in association with any scope of regulation under consideration, including the No Action alternative. The consequence of an exclusion is that the excluded item is no longer considered by APHIS to be a regulated article. APHIS envisions that the regulated community could apply for an exclusion, or an exclusion could originate within the agency itself. Exclusions would apply to classes of organisms based on the engineered trait. For example, one might exclude all organisms in which the only transgene expressed was a particular marker gene. The exclusion decisionmaking process would be fully documented and NEPA-compliant, and it would include opportunity for public comment.

Alternatives Related to Issue 1

1. No Action—continue to regulate GE organisms as potential plant pests, and use genetic transformation as the trigger for regulation (event-by-event).

2. Expand the scope of what is regulated by adding considerations of noxious weed risk and regulating GE biological control organisms in addition to evaluating plant pest risks, and use genetic transformation as the trigger for regulation. Continue to regulate event-by-event.

3. Expand the scope of what is regulated by adding considerations of noxious weed risk and regulating GE biological control organisms in addition to evaluating plant pest risks. Use novelty of the trait in the species as the trigger for regulation.

In addition, the following alternative could be used in conjunction with any of the above to exclude certain organisms based on risk:

4. Exclude specific classes of highly familiar organisms and highly domesticated, nonweedy crop plants and, potentially, those regulated by another Federal Agency from regulation.

2. Issue 2

APHIS is considering revisions to the regulations to increase transparency and to address advances in technology that may create new products and concerns. Should a new system of risk based categories be designed to deal with new products and new concern? If so, what criteria should be used to establish the risk-based categories?

There is public interest in understanding how APHIS regulates various types of organisms according to risk and familiarity. In addition, there is a trend toward more highly varied organisms, and the risk assessment process may need greater flexibility to handle this variety. The current system of notifications and permits needs to be more transparent to the public, and developers have a vested interest in knowing how organisms that they are developing will be regulated. In addition, the term "notification" has proven somewhat misleading in that it does not clearly convey that these introductions are subject to full APHIS oversight: no GE organisms may be imported, moved interstate, or released into the environment without active approval from APHIS. In recognition of the issues above, the agency is considering risk-based categories in which GE plants are classified according to risk and familiarity so that oversight and confinement vary by category. Redefined categories may provide added flexibility to better regulate diverse organisms and new types of traits and

provide better clarity to the regulated community and to the public, which may in turn promote greater confidence in the system.

APHIS currently uses a two-tiered approach to evaluate the risk of introducing GE plants. Introductions of GE plants that meet specific eligibility criteria based on their very low plant-pest potential can be authorized using the notification option, while plants that do not meet the eligibility criteria and all other types of organisms must use the permit option. The notification option has been an effective regulatory tool: the process features a simplified submission format, expedited agency review, and reduced regulatory burdens for both applicants and the agency while still ensuring safety. As part of the notification process, APHIS biotechnologists review all applications individually; APHIS requires effective confinement measures; all field releases are subject to inspection; and APHIS can impose severe penalties for noncompliance. Any new system that APHIS considers will incorporate salient aspects of the notification system to ensure the continued safe introduction of GE plants.

The types of organisms authorized under permit are highly varied, and the risk assessment process needs great flexibility to handle this variety. Within the class of organisms that require permits, there are subclasses such as micro-organisms, insects, and plants, including pharmaceutical and industrial plants, which do not meet the eligibility criteria for notification. Though each of these subclasses uses the same basic permitting procedure, reviews and assessment are done on a case-by-case basis and mandated permit conditions are unique for each permit. Pharmaceutical and industrial plants are subject to additional conditions, as detailed in the March 10, 2003, *Federal Register* notice (APHIS, 2003) and other guidance on the APHIS–BRS Web site.

APHIS is considering whether greater clarity will be provided by revising existing tiers and creating additional tiers, such that similar organisms could be grouped into tiers, thereby allowing for the applications and reviews to be structured in the most appropriate way for the organisms in that tier type. The appropriate tier for an organism expressing a transgenic trait or group of traits would be determined by various risk factors associated with the introduction of a particular GE organism. Similar to current practice, APHIS would consider several factors, including the biology of the organism, the nature of the transgenic traits expressed by the organism, the degree to which APHIS was familiar with the organism and the traits, and the size and duration of the introduction.

In scoping meetings held with stakeholders in January 2004, several industry representatives expressed a preference for a case-by-case review without tiers. Their opinion was that this approach was the most firmly

grounded in science because no preconceptions or assumptions entered into the evaluation. One example the stakeholders raised is the permitting of plants producing pharmaceutical or industrial substances. Placing a particular GE organism into a risk category because it produces a substance with pharmaceutical or industrial properties does not take into account the nature of the substance itself. For example, the substance may have already passed food-safety assessment by FDA and, therefore, likely poses no risks to the human environment. The stakeholders felt that a case-by-case evaluation reduces arbitrary placement into risk categories. It is not APHIS' intent to create risk categories that do not take into account the nature of the substance itself or to evaluate organisms based on preconceived notions or assumptions that are not grounded in science. The intent of creating a tiered system is to create greater predictability and transparency for both the regulated community and the public and to allocate agency resources effectively. A pure case by case approach would not meet APHIS needs, because it would be more difficult for the public and the regulated community to ascertain from the results of each determination whether there is a predictable and consistent method for the determinations,. In addition, this system would use more agency resources because even GE organisms with which APHIS has a great deal of experience would require a full, individualized analysis.

Alternatives 3 and 4, below, propose increasing the number of tiers to reflect the diversity of GE organisms that APHIS must evaluate. The difference between alternatives 3 and 4 is that the fourth alternative proposes to establish a separate permit type specifically for the regulation of nonplant GE organisms, for example, micro-organisms, insects, and other animals that can be plant pests. Tiers would be based on potential risks and familiarity with the organisms, and the degree of confinement and oversight would vary by tier type. As under the current system, the permit requirements could be tailored, based on APHIS' evaluation of the organism. Familiarity is important because unfamiliar organisms may pose risks that the agency does not currently recognize and with which the agency may have little mitigation experience.

Although APHIS currently sees very few permit applications for nonplant GE organisms, the agency recognizes that, based on advances described in the scientific literature, applications for the introduction of nonplant GE organisms may begin to increase. Increased numbers of applications and agency experience gained with nonplant GE organisms may, at some point, justify the creation of dedicated risk-assessment tiers for these organisms. Alternative 3 would require creation of tiers for plants and nonplant organisms alike in the revised rules, whereas alternative 4 allows for creation of tiers for plants while continuing to handle nonplant GE organisms on a case-by-case basis for the foreseeable future.

Alternatives Related to Issue 2

1. No Action—continue to use a two-tiered system (notifications and permits).

2. Abolish categories and treat all future proposals for the introduction of GE organisms on a case-by-case basis.

3. Establish a tiered permitting system for all organisms based on newly devised criteria.

4. Establish a tiered permitting system for plants based on newly devised criteria and evaluate permit applications for introductions of nonplant organisms on a case-by-case basis.

3. Issue 3

APHIS is considering ways to provide regulatory flexibility for future decisions by accommodating commercialization of certain genetically engineered organisms while continuing, in some cases, to regulate the organisms based on minor unresolved risks. Other regulated articles could be treated as they have been under the current system, in which all regulatory restrictions are removed. What environmental factors should be considered in distinguishing between these kinds of decisions?

Once an article has been deregulated, APHIS cannot place any restrictions or requirements on its use, short of re-regulating the article. Restrictions and requirements have not been deemed necessary in the past because BRS risk assessments have concluded that the GE plants APHIS has deregulated pose no greater risks than conventionally bred plants. However, APHIS recognizes that future development and commercialization of plants with less familiar traits may pose new challenges for the agency because even a thorough assessment may not resolve all unknowns regarding an article proposed for deregulation. These unknowns may justify continued scrutiny and data collection or use restrictions, even while allowing planting of the article without a permit. Therefore, APHIS is exploring a system that could give increased flexibility for handling special cases involving less familiar traits by creating provisions that allow for imposition of conditions for unconfined release. This could facilitate commercialization, while requiring appropriate restrictions or monitoring.

Under the current system, APHIS has not placed any restrictions or requirements on the use of a GE organism that has been fully deregulated because a GE organism is not fully deregulated until a thorough review concludes that it poses no plant-pest risks.

In evaluating the data submitted by the applicant, the agency considers the biology of the plant, potential interactions between the plant and the environment, and the nature of the inserted gene. Key biological features of the plant that are considered are whether it is an annual or perennial plant, whether it has sexually compatible relatives in the United States, whether the plant exhibits weedy characteristics, and how the plant is pollinated. The nature of the inserted gene is also considered. Some data requirements may relate specifically to the function of the gene. Other data requirements are more general and are aimed at determining whether the engineered crop has unanticipated characteristics that would render it phenotypically different than the non-engineered counterpart.

APHIS has deregulated more than 70 organisms representing 12 plant species. Although not every one of these organisms is being grown commercially, many of them have been adopted by farmers both in the United States and elsewhere (ISAAA, 2006). In spite of widespread cultivation of GE crops, there have been no reports of deregulated GE plants causing harm to agriculture or the human environment.

Most of the deregulated plants exhibit one of two traits—herbicide tolerance or insect resistance—and APHIS has extensive experience evaluating the agronomic and environmental impacts of these traits. APHIS has deregulated plants with other traits, such as viral disease resistance and altered fruit quality, and there most likely will be an increase in the types of trait–plant combinations proposed for deregulation.

The development of plants with less familiar traits may pose new challenges, and a thorough assessment may not resolve all unknowns regarding an article proposed for deregulation. These unknowns may justify continued scrutiny and data collection or restrictions on use. Therefore, APHIS is exploring partial deregulation to increase its ability to address risks by applying appropriate restrictions or monitoring requirements while accommodating commercialization.

Although APHIS has not approved the partial deregulation of any regulated article to date, a system in which partial oversight could be retained would allow the commercial production of a regulated article with appropriate restrictions or requirements. For example, an applicant may have geographically limited field-performance data for a crop intended for nationwide release. The placing of restrictions on the crop could enable the commercial sale and growth of the crop in regions where its performance is well documented but require that additional data be collected in specific geographic regions. This partial oversight might be accomplished under the current regulations by choosing to deregulate

in part or through some new regulatory mechanism designed specifically to deliver such flexibility. Another example where restrictions might be used to address a minor risk includes plants engineered for environmental remediation of heavy metals. Because of the potential environmental benefit, deregulation might be desirable; however, complete deregulation would be inappropriate due to the need to ensure proper disposal of plant material after remediation had occurred.

Currently, all deregulated GE plants can be used in breeding programs without regulatory restrictions. This is consistent with the findings that they pose no plant pest risks. Thus, if two deregulated plant lines with different traits are bred together or "stacked," the new line with the two traits combined is not regulated. Implementing a mechanism for partial deregulation might also give the agency a useful additional mechanism to place restrictions on certain stacked traits. While this has not been deemed necessary for the plant–trait combinations that have been deregulated to date, it might be a mechanism that could be deployed in the future for less familiar traits.

APHIS would use this mechanism only if there was a reason to believe there would be an interaction with certain other genes or traits that could result in environmental harm. In these cases, if a developer wanted to cross a partially deregulated plant with another variety that was not allowed under the terms of the deregulation, the developer might have to treat the offspring of the cross as a regulated article and additional review would be required before the new variety could be approved for unconfined release. This approach would allow APHIS to mitigate any additional potential environmental effects that might arise as a result of stacking of particular types of genes in certain plant species.

The proposed alternative would retain the option for full removal of agency oversight (currently obtained through deregulation), but also allow for a new option that allowed for a continued level of oversight as necessary to mitigate minor risks. The alternative would also allow the agency to conditionally approve petitions if to do so would mitigate any adverse environmental impacts that may result from the use of the article.

Alternatives Related to Issue 3

1. No Action—continue with a system granting full nonregulated status to crops that removes them from all regulatory obligations under 7 CFR part 340.

2. Continue to allow for the option of granting full nonregulated status and develop appropriate criteria and procedures through which crops

can be removed from permitting but some degree of agency oversight as necessary to mitigate any minor risks is retained.

4. Issue 4

Are there changes that should be considered relative to environmental review of, and permit conditions for, genetically engineered plants that produce pharmaceutical and industrial compounds?

Genetic engineering technology has advanced to the point where organisms can be developed that produce novel proteins and other substances with biological activity or industrial utility. The gene products made by pharmaceutical and industrial plants may have biological activity or may pose other hazards not associated with proteins and other substances commonly found in the food supply. APHIS will examine this issue in the DEIS, taking into account the current rigorous permit conditions, multiple annual inspections required for these plants, and the nature of the compounds produced by these plants. In practice, any changes in the confinement of plants producing pharmaceutical and industrial compounds would not apply solely to those plants, but to a risk tier that might include those plants.

Currently APHIS permit conditions prescribe various measures, used in combination, to create a confined field release. These measures can include:

- Geographic isolation of the field test from other growing crops,
- Temporal (time of planting) separation of the field test from plants of the same species to prevent simultaneous availability of viable transgenic pollen and receptive flowers outside the test plot,
- Physical barriers to gene flow (e.g., bagging flowers),
- Biological barriers to gene flow (e.g., male sterility), and
- Requirement for dedicated planters and harvesters and APHIS-approved cleaning protocols for other equipment

The measures are crop-specific and are determined by plant biology factors, such as whether the plant is an annual or perennial, whether it has sexually compatible relatives in the United States, whether the plant exhibits weedy characteristics, and how the plant is pollinated. In addition to the stringent permit conditions, multiple annual inspections ensure compliance.

For example, if corn is used to produce a pharmaceutical substance and an applicant wishes to perform a field test of this plant, no other corn may be grown within 1 mile of the field-test site (68 FR 11337). This distance is eight times the distance required in the production of foundation corn

seed. In APHIS' experience, plants expressing pharmaceutical or industrial traits are no more likely to escape from field tests or persist in the environment than plants expressing other traits. However, it has been suggested that plants engineered to produce substances not intended for food use, as handled under APHIS' current regulatory system, pose unacceptable risks to human health, the environment, and to trade.

Several alternatives to address this issue are under consideration. Alternative 2 is a variation on the No Action alternative in which GE plants producing proteins or other substances whose safety has not been addressed would have much more restrictive requirements for outdoor testing, but would not be banned from consideration for outdoor testing. Alternative 3 is the most restrictive approach to GE plants producing pharmaceutical or industrial substances, namely that no such plants would be considered for outdoor testing. The only way these plants could be grown would be under contained conditions, for example, in enclosed growth chambers or other facilities such as abandoned mines, so that environmental releases are highly unlikely. A corollary of this approach, Alternative 4, is that no plants producing pharmaceutical or industrial substances may be released into the environment if that plant species is used for food or feed purposes. Nonfood or nonfeed plants expressing pharmaceutical or industrial traits could be field tested under an APHIS permit but with stringent conditions.

In Alternative 5, field tests of nonfood or nonfeed plants would be allowed under APHIS permit, and field tests of food or feed crops would also be allowed if the food safety issues have been addressed. This review would guarantee that, should the confinement measures used with an APHIS-permitted field test fail, any escape of the plant from the test site would not result in any significant harm to humans or the environment.

Alternatives Related to Issue 4

1. No Action—continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds and to allow field testing under very stringent conditions.

2. Continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds. The agency would impose confinement requirements, as appropriate, based on the risk posed by the organism and would consider food safety in setting conditions.

3. Do not allow crops producing substances not intended for food uses to be field tested, that is, these crops could be grown only in contained facilities.

4. Allow field testing only if the crop has no food or feed uses.

5. Allow field testing of food/feed crops producing substances not intended for food uses only if food safety has been addressed.

5. Issue 5

The definition of noxious weed in the PPA includes not only plants, but also plant products. Based on that authority, APHIS is considering the regulation of nonviable plant material. Is the regulation of nonviable material appropriate and, if so, in what cases should we regulate?

In some special cases, certain nonviable material originating from a field test (e.g., cell debris, leaves, stems, roots, or seeds) may pose unique types of environmental or human health risks. Currently, APHIS regulates organisms that pose a plant pest risk and does not regulate nonliving material derived from GE organisms. By definition, plant pests are living organisms. However, the noxious weed definition provides authority to regulate nonviable plant products that could "injure or cause damage to crops." Because there may be cases in which potential risks could justify the regulation of nonviable material, APHIS is considering whether it should regulate nonviable material in those cases.

The agency considers non-living material generally not to be a significant risk to the environment because non-living material cannot result in the dissemination or persistence of GE organisms. Most, if not all, field tests of GE organisms conducted under an APHIS permit result in nonviable material being produced in the form of nonpropagable GE material (e.g., cell debris, leaves, stems, or roots) in addition to the desired product (e.g., seeds). The desired product is removed by the researcher, and byproducts are disposed of according to the terms of the permit, which may include such methods as autoclaving, placing in a landfill, burying, plowing into the soil, or burning. The purpose of these processes is to ensure that any residual propagable material is destroyed so that it cannot escape into the environment at large. The current regulations focus on the destruction of viable propagules as these items have the potential to produce a new generation of the organism.

The noxious weed definition in the PPA includes plants as well as plant products thus providing an opportunity for APHIS to expand its regulatory scope. This does not mean that APHIS has determined that all GE plants are noxious weeds, but this would allow the agency to ascertain if the nonviable material could pose agricultural or environmental harm. Therefore, APHIS is considering whether it might be advantageous (e.g., in cases where permit conditions had been violated or when the nonviable

material was determined to be toxic) to regulate nonviable material that might pose an environmental risk.

Alternatives Related to Issue 5

1. No Action—do not regulate nonviable GE material.

2. Regulate nonviable GE plant material in certain circumstances, based on the risks posed.

3. Regulate all nonviable GE plant material.

6. Issue 6

APHIS is considering establishing a new mechanism involving APHIS, the States, and the producer for commercial production of plants not intended for food or feed in cases where the producer would prefer to develop and extract pharmaceutical and industrial compounds under confinement conditions with governmental oversight, rather than grant nonregulated status. What should be the characteristics of this mechanism?

For organisms that cannot meet the criteria for deregulation, APHIS is considering whether a new type of permitting system would be more appropriate in terms of efficiency and effectiveness than the current system. In addition, there is much public and State interest in these types of plantings and a new mechanism may increase transparency and allow for greater State involvement.

Currently, GE plants producing pharmaceutical or industrial compounds or expressing other traits not intended for food/feed uses have not been deregulated. APHIS anticipates that field tests for these plants would likely be conducted annually, in the same location, and under the same permit conditions each year; however, APHIS' regulations require a full permit application for these plants year after year and repeatedly reviewing identical annual applications would be very inefficient. A new type of permitting process could continue to ensure safety but increase the efficiency of issuing annual permits for repeating field tests. This mechanism might also apply to other types of GE organisms or appropriate activities, such as repetitive research.

Due to the value of the pharmaceutical or industrial substances synthesized by these plants, after the plants are harvested under APHIS-approved permit conditions; the valuable substance may be extracted from the plant material, and the substance may be sold commercially. It is possible and even likely, that many of these substances do not pose a human-health risk in food and also that they do not pose a risk to

agriculture or the environment. However, some of these substances may be allergenic, toxic, or otherwise biologically active in humans and APHIS requires extraordinary safeguards to ensure that they are not found in commodity food or feed channels.

Alternative 2 would create a new permitting process, which begins with the submission of a full permit application for the first annual cycle of the field tests. This application would receive full APHIS review, permit conditions and confinement measures would be prescribed, and, if all regulatory requirements are met, the permit would be issued. For subsequent years, the applicant would submit a multiyear plan that integrates all standard operating procedures (SOPs) and all management practices designed to confine the planting and minimize its potential to cause environmental impacts. After APHIS review and approval of the management plan, the applicant would be issued a multiyear permit designed specifically to address the needs and issues surrounding production. APHIS would also consider measures such as Quality Control/Quality Assurance procedures, ISO quality management standards, and other technical standards, if appropriate. The applicant would be required to conduct the field release in all subsequent years exactly as prescribed in the permit. APHIS would monitor SOPs for repetitive activities. Any changes to the original permit application or approved SOPs would have to be submitted to APHIS for approval prior to implementation. These fields would still be subject to inspection. Also, APHIS would rely on additional auditing to ensure compliance with all conditions and to ensure activities are conducted according to approved SOPs.

Alternatives Related to Issue 6

1. No Action—continue to authorize field tests of crops not intended for food or feed use under permit. Require application and review of these permits on an annual basis.

2. Allow for special multi-year permits, with ongoing oversight. The new system would maintain these crops under regulation, but APHIS oversight would be exercised in a different manner than under the current system of permits.

7. Issue 7

The current regulations have no provision for the low-level presence of regulated articles in commercial crops, food, feed, or seed of GE plant material that has not completed the required regulatory processes.[11] Should low-level occurrence of a regulated article be exempted from regulation?

As with traditional plant breeding, large scale annual field testing of GE plants that have not completed all applicable reviews may result in materials from these trials occasionally being detected at low levels in commercial commodities and seeds. Current regulations do not expressly allow for any such occurrence, though experience continues to show that such occurrences can occur. In a 2002 Office of Science and Technology Policy (OSTP) notice,[12] APHIS committed to conducting a risk-based regulatory program that minimizes the occurrence of these materials and includes safety criteria under which these materials would be allowed at low levels in commercial commodities and seeds.

Adventitious presence in the NOI referred to low levels of biotechnology-derived genes and gene products occurring in commerce that have not gone through all applicable regulatory reviews. However, APHIS realizes that this term means different things to various interests around the world; hence, its use elsewhere in the main body of the EIS will be avoided. Many groups, including some importers of U.S. agricultural products, use the term to refer to the presence of any biotechnology-derived products when found in a product that is intended to be free of such materials, even when the biotechnology-derived products completed deregulation by APHIS and all other applicable reviews. Once the materials have completed all applicable reviews, they are considered as safe as other non-GE varieties and, as such, are not regulated. Thus, APHIS views the presence of deregulated materials as a marketing issue outside of its authority.

In practice, APHIS has considered these situations on a case-by-case basis and believes there are situations in which occurrence of regulated material at low level should be non-actionable, meaning that commodities or seeds with the low levels of the regulated articles could be moved and otherwise introduced without a need for permits or notifications. These determinations are based on safety and might be made in cases where the material is similar to a deregulated GE organism and APHIS determines that the presence of the regulated material does not pose a plant pest risk.

[11] In the NOI, the term *adventitious presence* was used to refer to the "intermittent low levels of biotechnology-derived genes and gene products occurring in commerce that have not gone through all applicable regulatory reviews." However, APHIS realizes that this term means different things to various interests around the world; hence, we will avoid its use elsewhere in the main body of the EIS.

[12] 67 FR 50577

In other instances, in which the regulated material is very different from any deregulated GE organisms and there may be a potential plant pest risk, APHIS has determined that any amount would be considered actionable and the agency would act as necessary under the regulations to prevent dissemination of the regulated material. In all cases, APHIS completes a risk assessment to determine the agency response. It is important to note that under the current system and any proposed revision to the system, the developer is still responsible for complying with regulations. Thus, the material might be safe and non-actionable, but the developer might still be found to be in violation and subject to penalties. On March 29, 2007, APHIS published its Policy on Responding to the Low-level Presence of Regulated Genetically Engineered Plant Materials in the *Federal Register* (72 FR 14649).

APHIS and the U.S. government have been aware for some time that the occasional detection of regulated material in commercial crop seeds is a potential outcome of field tests conducted under experimental protocols generally used for notifications. This is due to cross pollination and also commingling from shared equipment and facilities. In the majority of cases, this low level occurrence will be of minimal risk, and this should be accounted for in any regulatory scheme since oversight should be commensurate with risk. In addition, new incidents will inevitably result from the importation of seeds and commodities from countries where such material has been fully approved but has not completed all U.S. reviews.

There have been several incidents where regulated articles have been detected in commodities or seeds. In one of the first, the agency became aware that there were low levels (<1 percent) of plant varieties that had not been deregulated in the United States in imported seeds. These varieties were evaluated by FDA to determine that there were no food-safety issues. The seeds were genetically engineered to be herbicide tolerant, and the imported varieties were very similar to a variety that had been deregulated in the United States. The developer filed extension requests (7 CFR § 340.6(e)) that, if granted by APHIS, would result in nonregulated status being extended from a previous deregulation to cover the imported varieties as well. While intended to be an expedited review, the required data package and established review practices are such that extension requests can be similar in terms of regulatory burden to regular petitions for nonregulated status. The extension requests for the crop were granted, but it became apparent that it would be advantageous to have a policy for dealing with low-level presence of regulated articles that met certain safety criteria.

In another case, a company found that some of their breeding lines being used for production of commercial seed were, in fact, a different line that

had not been deregulated. However, as with the previous example, the line that had not been deregulated was very similar to a line that had already been deregulated. All expressed proteins were identical. In this case, USDA quarantined the seeds and EPA issued a "Stop Sale Order" to halt commercial sales of seed for planting and restrict seed movement except for specifically identified regulatory needs or destruction. USDA, in conjunction with EPA, undertook an extensive investigation into the unauthorized movement, release, and sales of the corn seeds for planting. The company was required to remove all seeds from the commercial sales channel, and APHIS provided regulatory oversight for the destruction of the remaining stocks. Based on its own safety assessment, which concluded that there were no safety issues, APHIS decided that it would not attempt to remove any low levels of this variety that might exist in commodities.

In yet another case, a small number of volunteer plants from a previous field test were harvested with a subsequent crop resulting in a very small amount of regulated debris in the harvested crop. In this case, APHIS considered this debris as unacceptable because of the nature of the protein involved. Accordingly, the agency took action to ensure that the crop was quarantined and subsequently destroyed.

APHIS recognizes the need for a clear regulatory approach to address the science issues described above, and many stakeholders have advocated that establishing this policy should be a very high priority for APHIS.[13] These stakeholders include industry associations, crop associations, and commodity trade organizations. Also, in August 2002, the Office of Science and Technology Policy initiated the coordination of a Government-wide approach involving the establishment of early food-safety assessments at EPA and FDA, and the revision of APHIS' field testing program.

APHIS has already made some important changes. Permit requirements for the field testing of plants with genes producing pharmaceutical compounds have been strengthened significantly, as announced in the March 10, 2003, *Federal Register* notice (APHIS 2003). Plants with genes producing industrial compounds are now subject to the permitting system as described in the August 6, 2003, interim rule (finalized on May 4, 2005), whereas, some of these plants previously qualified for field testing under notification. Pharmaceutical and industrial plants are confined with such stringency that their testing and production is not expected to result in detection in commercial products.

[13] On March 30, 2007, APHIS published its "Policy on Responding to the Low-Level Presence of Regulated Genetically Engineered Plant Materials (http://www.aphis.usda.gov/brs/fedregister/RBS_20070330a.pdf).

APHIS would generally consider any presence of materials engineered for pharmaceutical or industrial uses as actionable, but changes might be possible under the new regulations for specific organisms such that they could be reclassified based on safety. Thus, if the regulated gene products have been reviewed for food safety and meet the criteria that APHIS establishes in the revised regulations, presence of the material may not be cause for agency action. The safety criteria that APHIS establishes will be applied to any such occurrence of a regulated article, regardless of whether it occurs in commodities or seeds that are domestic or imported. The goal of revising APHIS regulations on this issue is to create a uniform policy for regulated gene products so that public, foreign, and domestic stakeholders can be assured of the safety of any gene product that occurs at low levels in commercial commodities and seeds.

Alternatives Related to Issue 7

1. No Action—allow field testing to continue using current confinement strategies to reduce the likelihood of regulated articles occurring in commercial commodities or seeds.

2. Establish criteria under which occurrence of regulated articles would be allowable, that is, considered not-actionable by APHIS. Do not allow field testing of crops that do not meet all of criteria, including addressing food safety issues if applicable (i.e., if the GE plant is a food crop).

3. Establish criteria under which occurrence of regulated articles would be allowable, that is, considered not-actionable by APHIS. Allow field testing and impose confinement strategies based on whether a plant meets the criteria.

4. Impose a very strict confinement regime on all field tests, as is currently done for pharmaceutical and industrial crops that would further reduce the likelihood of regulated articles occurring in commercial commodities or seeds.

8. Issue 8

Should APHIS provide expedited review or exemption from review for certain low-risk, imported GE commodities intended for food, feed, or processing that have received all necessary regulatory approvals in their country-of-origin and are not intended for propagation in the United States?

APHIS anticipates an increasing number of requests to import regulated GE organisms that are not intended for propagation, such as organisms that are intended for direct use as food, feed, or for processing. The

current regulatory system was designed to handle such requests using permits and notifications. However, in anticipation of this increase, APHIS' goal is to design an efficient system that protects U.S. agriculture and human health without erecting unnecessary trade barriers. To that end, the agency has evaluated several different alternatives.

APHIS recognizes the need to reevaluate requirements for imported commodity shipments containing GE plant products that are intended for food, feed, or other uses and not intended for propagation. APHIS requires an importation permit for GE plants for food, feed, or for processing, such as canola for processing into oil and feed, or fresh fruits and vegetables for direct consumption if they have not been deregulated. However, because these materials will be used only for nonpropagative purposes, they can be presumed to pose less risk to agriculture than an equivalent crop intended for large-scale planting due to the reduced magnitude of environmental exposure. On rare occasions, APHIS has allowed certain materials to be imported, on a case-by-case basis, for nonpropagative purposes if the agency is familiar with the plant-trait combination, and determines that the intended use poses a low risk of environmental harm and environmental persistence.

In reevaluating its regulations, APHIS recognizes that in many cases it may not be necessary to perform full environmental risk assessments for GE plants imported for nonpropagative uses to ensure environmental safety, recognizing that other safety issues may also be subject to EPA and FDA oversight. Because these materials are not intended for field testing, it is an inefficient use of APHIS resources to subject them to the same scrutiny given materials proposed for full deregulation. An appropriate risk assessment could be based on APHIS' familiarity with the GE trait, the biology of the plant, its intended use, proposed containment measures, and any environmental review data generated by the exporting country's regulatory body.

In addition to domestic environmental concerns, APHIS recognizes that regulations on imported commodities have international implications. For example, the Cartagena Protocol on Biosafety (CPB) (http://www.biodiv.org/biosafety/default.asp) is an international treaty that provides a framework for the safe transboundary movement of living genetically modified organisms (LMOs) with the goal of protecting biodiversity. While the United States is not a party, U.S. exporters need to comply with regulations implemented by importing parties in accordance with the CPB. Currently, distinctions are made within the CPB between the importation of LMOs intended for intentional introduction into the environment and LMOs imported only for food, feed, or for processing (LMOFFPs), and the Protocol describes a separate, less burdensome

procedure governing the importation of LMOFFPs. The different procedures set out under the CPB reflect the understanding that these imports will generally pose a substantially lower potential risk to the environment or to biodiversity than LMOs intended for field testing.

APHIS needs to consider how its regulatory changes might coordinate or conflict with existing international agreements related to agriculture, food, or trade. At the same time, APHIS needs to continue to provide leadership for countries in the early stages of developing their own regulations.

Alternatives Related to Issue 8

1. No Action—continue to evaluate commodity importation requests on a case-by-case basis.

2. Establish criteria that will be applied to determine the appropriate level of risk assessment for imported GE commodities. This alternative could include a decision to exempt certain organisms or to allow importation under conditions that minimize environmental release.

3. Disallow importation of any commodity pending full APHIS approval for deregulation.

4. Accept any importation of a product from a foreign country that has evaluated the safety of the product and approved it for unconfined environmental release.

5. Accept any importation of a product from a foreign country that has evaluated the safety of the product and approved it for unconfined environmental release using a review process equivalent to APHIS'.

9. Issue 9

Currently, genetically engineered *Arabidopsis* spp. are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. Should the movement of genetically engineered *Arabidopsis* spp. or other GE organisms be exempted from movement restriction?

Currently, genetically engineered *Arabidopsis* spp. and a few other organisms are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. The agency is considering whether to expand the current exemption from interstate movement restrictions to other well-studied, low-risk, GE research organisms. Such a change would create a consistent, risk based approach to organisms with similar risk profiles.

The 2002 NRC report entitled *Environmental Effects of Transgenic Plants: The Scope and Adequacy of Regulation* (NRC, 2002) cited the need to focus regulatory oversight on GE plants that pose the highest risk while not placing unnecessary burdens on those posing low risk. APHIS recognizes that it is important to find ways to reduce regulatory costs and burdens when risk is low. One approach is to expand the provision for unregulated interstate movement of certain well-studied research organisms that present little, or no environmental risk. Such an action would be based on risk and available scientific data. This expansion could offer substantial regulatory relief to small startup companies, public institutions, and academic researchers, whose resources are often strained to comply with regulations for GE organisms.

Alternatives Related to Issue 9

1. No Action—Require interstate movement authorizations for all organisms on the list in 7 CFR § 340.2(b).

2. Exempt a class of GE plants or organisms that are well-studied and present little or no environmental risk from permit requirements for interstate movement as is currently done for *Arabidopsis*.

3. Create a process to apply for an interstate movement exemption for a particular species.

10. Issue 10

What environmental considerations should be evaluated if APHIS were to move from prescriptive container requirements for shipment of GE organisms to performance-based container requirements, supplemented with guidance on ways to meet the performance standards?

APHIS regulations prescribe the use of several types of packaging to prevent the escape, dissemination, and environmental persistence of GE organisms. However, based on APHIS' experience there are other types of containers that can be used to safely move GE organisms. APHIS often grants applicants a variance to use a different container to transport a GE organism in a way other than prescribed by the regulations but reviewing these requests takes agency resources. APHIS is considering alternatives that will reduce the need for variances but still facilitate the safe movement of GE organisms.

Alternative 2, below, proposes to replace the current list of prescribed transport containers with performance standards for all containers used to move regulated articles. In other words, rather than describe in the regulations how containers must be constructed, APHIS would specify

what the containers must do and how they must perform, namely they must prevent spillage, leakage, escape, and other environmental releases of regulated articles. Having performance standards for transport containers would obviate the need for variances and would therefore reduce the burden on applicants as well as increase the efficient use of APHIS resources. The regulated community would be responsible for the design of appropriate containers that will prevent environmental releases. Each applicant would certify that the proposed transport containers will meet APHIS performance standards. The use of containers that fail to meet those standards will result in an APHIS enforcement action.

Alternative 3 proposes to add new APHIS approved containers to the current list in the regulations, thus reducing the number of variance requests that must be processed and reducing the regulatory burden on applicants. These new container types could reflect the specialized needs of applicants who would in the past have been forced to ask for a variance.

Alternatives Related to Issue 10

1. No Action—retain current list of approved containers and issue variances when necessary.

2. Switch to performance-based standards for all transport containers.

3. Expand current list of approved containers and issue variances when necessary.

C. Alternatives Rejected From Further Consideration

APHIS assembled a comprehensive list of regulatory alternatives and alternatives that might be implemented in the regulatory revision process. The original list of alternatives was intended to be inclusive rather than selective, so initially APHIS considered all ideas. The agency individually evaluated each alternative on the basis of legality, environmental safety, efficacy, and practicality to identify which alternatives would be further considered during rulemaking. Based on this evaluation, APHIS rejected several alternatives. In the interest of transparency, these alternatives are discussed briefly below along with the specific reasons for rejecting each.

One regulatory alternative that APHIS considered but rejected was not to regulate GE organisms at all. FDA and EPA would continue to examine the impacts of the subset of GE organisms over which they have authority, but APHIS would no longer consider the risks to U.S. agriculture posed by

the release of GE organisms. APHIS is forced to reject this alternative as unreasonable due to a clear Congressional mandate as stated in the PPA—

> "…the unregulated movement of plant pests, noxious weeds, plants, certain biological control organisms, plant products, and articles capable of harboring plant pests or noxious weeds could present an unacceptable risk of introducing or spreading plant pests or noxious weeds… § 402(7)."

Without APHIS oversight, GE organisms with the capability of becoming plant pests or noxious weeds could be released, thus causing an "unacceptable risk" to the practice of agriculture in the United States. Allowing such risks would be a clear dereliction of APHIS' congressionally designated duty. The proposed wholesale deregulation of all GE organisms must, therefore, be rejected.

The opposite alternative, which APHIS considered but also rejected, was that the release of all GE organisms be forbidden. APHIS determined that this alternative is unreasonable. GE corn, soybeans, and cotton plants that have completed the deregulation process are planted on more than 100 million acres in the United States. GE crops are grown on more than 200 million acres worldwide. A ban of all GE organisms would necessitate a complete restructuring of American agriculture as well as the seed industry and cause profound disruption of international trade in agricultural commodities. These crops are regarded as safe based on experience and the potential benefits that they bring to agriculture would not be realized if there was a complete ban. Lastly, such a ban would contravene clear congressional directives in the PPA. The Secretary of Agriculture is directed, through APHIS, to facilitate—

> "… the smooth movement of enterable plants, plant products, biological control organisms, or other articles into, out of, or within the United States… (and to facilitate) exports, imports, and interstate commerce in agricultural products and other commodities that pose a risk of harboring plant pests or noxious weeds in ways that will reduce, to the extent practicable, as determined by the Secretary, the risk of dissemination of plant pests or noxious weeds… § 402(3)(5)."

The question as to how to balance this facilitation with the protection of U.S. agriculture is unequivocally answered by Congress, which states that—

> "…decisions affecting imports, exports, and interstate movement of products regulated under (the Plant Protection Act) shall be based on sound science… § 402(4)."

A risk-management process based on sound science must, therefore, consider a growing body of scientific evidence documenting the safe use of GE organisms in U.S. agriculture, and in the rest of the world, to determine whether their use poses any unacceptable risks. Because Congress has mandated a science-based approach in APHIS regulations and because there is no basis in science for banning all uses for GE organisms, a blanket ban of GE organisms would contravene congressional intent and must be rejected.

APHIS rejected two other alternatives because they removed all APHIS oversight of important issues, risking serious compromise of environmental safety. The first of these involved the regulation of imported GE plants. It was proposed to allow the exporting country alone to determine the safety of GE commodities imported into the United States. APHIS concluded that delegating all authority to the exporting country, regardless of that country's regulatory scheme for GE organisms and its ability to implement those regulations, would create an unacceptably high risk that an organism with which APHIS was unfamiliar could be imported and cause significant environmental damage. Similarly, APHIS rejected an alternative to allow permit applicants to select any transport container, at their discretion, for the interstate movement of GE organisms. APHIS oversight of transport containers is crucial to the safe interstate movement of GE organisms. This oversight is most effective and efficient if exercised early in the movement process, when specifying the criteria for transport containers.

Finally, APHIS considered and rejected alternatives for dealing with the interstate movement of well-studied, low-risk research organisms because they provided incomplete solutions. APHIS considered two alternatives—one dealing solely with exemptions for specific GE plants and one dealing solely with exemptions for specific micro-organisms. Either of the alternatives could be adopted, but neither dealt with the issue in its entirety. APHIS deemed a provision dealing with both groups of organisms more effective.

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III. Affected Environment

Under the Plant Protection Act, APHIS has been authorized to regulate the importation, interstate movement, and environmental release (field testing) of GE organisms that are potential plant pests, GE organisms that are potential noxious weeds and GE organisms that are biological control organisms. The importation and interstate movement of GE organisms are extremely unlikely to affect the environment because the organisms remain under containment throughout the process. The release of GE organisms into the environment, under APHIS oversight, may result in environmental effects.

It is possible for the APHIS-authorized field testing of a GE organism to occur, with appropriate conditions to ensure confinement, in any U.S. State, commonwealth, or territory. Therefore, the geographic extent of the affected environment under consideration in this DEIS is the entire United States and its territories. Environmental releases of regulated articles will occur in discrete locations known by APHIS, under conditions designed to confine the article to the field test site. If APHIS deregulates a GE organism, the organism could be released anywhere in the United States because APHIS considers a deregulated GE organism to pose no plant pest risks.

This chapter introduces those aspects of the natural and physical environment, as well as interrelated socioeconomic factors that may be affected by the current regulations administered by APHIS–BRS as well as the alternatives as described in this DEIS. Chapter IV.A further discusses and analyzes, in depth, those issues identified by the agency and by the public and other stakeholders during scoping, including aspects of the environment that have the potential to be significantly affected by current or proposed APHIS–BRS program activities. The following topics will be presented in this chapter:

- Plants
- Insects and animals
- Agronomic practices
- Micro-organisms
- Socioeconomic issues

Plants—Plants engage in numerous physical and biochemical processes which affect humans and the environment. Plants produce food and fiber for humans and for animals, both domesticated and wild. Plants alter the atmosphere, removing carbon dioxide from the air and adding oxygen. They modulate air and soil temperature and create microenvironments for

other organisms. Plants modify soil structure through root growth and stabilize soil, thus reducing erosion, and plants add organic matter to the soil which feeds micro-organisms and improves soil quality. Plants also interact with each other by competing for sunlight, water, and soil nutrients. In addition, plant reproduction affects the environment through the release of pollen, fruits, and seeds. Weeds are plants which can compete so effectively with crop plants that they may reduce the value of the crop. Plants produce a large variety of chemical substances that may affect the local environment or provide economic value to humans. Like classical breeding, genetic engineering can alter the value of a plant to humans and may also affect one or more of the physical or biological interactions between plants and their environment.

Insects and Animals—Many insects and other animals are intimately associated with plants. These associations can be harmful, as in the case of animals that feed on plants, causing injury or even the death of the plant, resulting in economic losses. There are also positive associations—animals like bees and hummingbirds pollinate plants, and ladybugs eat harmful insect pests. In other cases, the association may be neutral, that is, the animal may merely live on or near the plant. GE traits in plants may alter these associations or create new ones.

Agronomic Practices—The vast majority of plants that APHIS has permitted for field testing, and ultimately deregulated, have contained GE traits, specifically, herbicide tolerance and insect resistance, that directly affect agronomic practices, that is, the methods a grower uses to grow the crop. As GE crops continue to be developed, APHIS expects many new traits to be expressed such as ones affecting nutritional quality, ones enabling environmental stress tolerance, and new traits for disease or insect resistance or herbicide tolerance. Some of these traits, like those affecting nutritional quality, may have little or no impact on agronomic practices. Others, like those for stress tolerance, may markedly affect how crops are grown. For example, a drought-tolerant crop could change how a farmer manages soil water. Drier fields could, in turn, affect insect pest populations and disease prevalence and, thus, further alter how the farmer manages the crop. Novel disease resistance, insect resistances, or herbicide tolerance traits could be expected to alter agronomic practices much in the same way as the currently available traits do, that is, some practices would change in frequency, others may be eliminated, and some new practices may be added, depending on the trait.

Micro-organisms—Plants also have a variety of interactions with micro-organisms. Certain soil microbes, like *Rhizobium* bacteria and some fungi, associate with plant roots and provide additional nutrition to the plants via various mechanisms. Conversely, many micro-organisms

(bacteria, fungi, and viruses, among others) cause serious plant diseases, resulting in enormous economic losses. There are also neutral associations—many yeasts, for example, live on plant leaves without causing any harm to the plant; other micro-organisms help decompose dead plant material in the soil. Creating disease-resistant plants through genetic engineering could change some of these negative associations but other GE traits, such as those affecting nutritional quality or plant structure, could alter other plant-microbe interactions.

Socioeconomics—Although most Americans are not producers of agricultural commodities, the availability, variety, price, and safety of food and fiber crops affects the lives of all Americans. By extension, changes to the methods of agricultural production in the United States may also affect anyone who produces, sells, processes, or consumes these products. Beyond ensuring that GE crop plants pose no plant pest risks, APHIS needs to consider and address, when appropriate, the social, cultural, and economic effects resulting from any significant environmental impact of regulating GE plants and from changing APHIS' regulatory approach.

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IV. Environmental Consequences

In the United States, genetically engineered (GE) organisms have been field-tested since the 1980s and grown commercially on millions of acres since the mid-1990s. Developers and researchers monitor field tests while growers, extension agents, and researchers scrutinize commercially grown GE crops. The Animal and Plant Health Inspection Service (APHIS) is not aware of any verifiable reports of environmental harm or harm to human health resulting from such field tests or from commercial use of GE plants.

The agency recognizes, however, that it cannot make general conclusions about the safety of GE organisms based on the existing body of science. In addition, new technology can lead to the development of novel types of GE organisms that may have a greater propensity for environmental impact, both positive and negative, than those field-tested to date. Therefore, even though past environmental releases have been conducted safely and commercial products are being safely grown and consumed, APHIS will continue to rigorously scrutinize new scientific developments as well as the potential environmental impacts of any proposed changes in its regulations.

This chapter examines how the implementation of current APHIS biotechnology regulations and possible changes in them might impact the quality of the environment.[14]

Section A of this chapter provides general background information for nonspecialist readers to better understand the discussions that appear later in the document. This section is divided into four subsections:

- Section A.1 provides an overview of plant and seed biology and concludes with a general discussion of the future of agricultural plant biotechnology.

- Section A.2 provides a general introduction concerning how the potential effects of GE organisms on the environment are typically assessed.

- Section A.3 discusses general topics relevant to the consideration and risk assessment of GE plants.

[14] The scientific information in this chapter was subjected to a peer review in accordance with guidance issued by the Office of Management and Budget and by the USDA. For more details about the peer review process for this draft EIS and for the peer review process in general, please see <http://www.aphis.usda.gov/peer_review/peer_review_agenda.shtml>.

- Section A.4 closes this chapter with further illustrations of how potential impacts of GE plants on the human environment are assessed. This subsection discusses several examples of GE modifications for specific plant qualities. Accompanying these examples are brief descriptions of some of the risk assessment issues associated with each of the modifications.

Section B of this chapter describes the regulatory features of APHIS' current system and how these features function together to reduce the likelihood of significant negative impacts.

Section C of this chapter describes the impacts of the individual No Action alternatives with respect to 10 specific issues. For each issue, the No Action alternative is followed by an analysis that compares it to one or more alternatives for new approaches.

A. Impacts of Genetically Engineered Organisms

1. Introduction to Biological Factors

This subsection briefly introduces the general ways in which plants, animals, insects, and micro-organisms affect the environment. Because GE plants currently comprise most of the releases of GE organisms into the environment, this subsection provides a general introduction focused on two broad plant related topics: 1) plant biology and crop improvement and 2) seed biology and commercial seed production.

a. Plant Biology and Crop Improvement

Plants exist in agricultural, managed ecosystems and wild, unmanaged ecosystems, and they interact with the environment in both (Janick et al.,1981). What follows is a summary of basic plant interactions in three defined contexts—the physical environment, the physiological environment, and the ecological environment.

The discussions are brief and broad but provide a basis for understanding how plants function in the environment and why plant breeders are attempting to modify those functions. Generally, breeders are attempting to enhance plant performance, which relates to a plant's ability to benefit from its positive interactions with the environment while suffering minimally from negative interactions (Allard, 1964).

For this discussion, genetic engineering is considered one tool among others that are available to plant breeders to add a desirable trait to a plant variety.

(1) Physical Environment

Except for parasitic plants, which grow partially within other plants, and epiphytic plants, which grow on other plants, most plants grow partially embedded in soil or in or on water. Many plants are capable of limited directional growth but most plants cannot move large distances (Wareing and Phillips, 1981); therefore, they are forced to obtain nutrients and water from nearby sources.

Terrestrial plants produce roots to absorb water and nutrients from the soil and to anchor themselves physically in the soil, but roots also directly affect the soil. Roots create spaces in soil for the passage of air, water, and soil organisms. In addition to these physical changes, roots release organic compounds which alter nutrient availability and accelerate soil development. As roots die and decompose, they contribute organic matter to the soil, improving its texture and its ability to retain water and nutrients. Plant roots also anchor soil particles and reduce soil erosion (Brady, 1974).

Plant breeders are frequently interested in developing varieties with robust growth, including root growth. Root-growth traits may alter nutrient absorption and drought tolerance but may also affect soil water distribution and irrigation practices and possibly soil stability and erosion. Among the GE traits currently under APHIS' oversight, only a few have the purpose of altering plant morphology. However, APHIS anticipates that altered morphology traits may be developed by researchers more frequently in the future.

Because adequate water is essential for survival and growth, plants have developed elaborate systems to absorb, transport, and retain water (Janick et al., 1981). Although roots can grow toward sources of soil water, soil water generally can move in the soil faster than roots can grow to reach it. Plants, therefore, use their own tissues to store water when it is readily available and use various means, such as waxy leaf coatings, to restrict water loss when water is not available (Esau, 1977). Some water loss is unavoidable, however; and through transpiration, plants lose water from aboveground surfaces and convey water from the soil into the air.

Depending on the environment to which a plant is adapted, too much or too little water may be harmful or fatal. Some plants have adapted the means to temporarily withstand flooding or drought, and plant breeders are actively working on developing these traits in crop plants in order to enable crop production in areas with less than optimal water availability. Drought tolerance may increase the range of environments where a crop or

wild plant can grow successfully and alter water management practices for growers.

Green plants have a profound affect on the Earth's atmosphere. As a result of photosynthesis, plants remove carbon dioxide from the air and produce carbohydrates, which plants use as their primary form of stored energy, as well as to increase biomass. The oxygen produced as a byproduct of photosynthesis is released by plants back into the atmosphere. Plants also reverse this process when carbohydrates are utilized for energy, producing carbon dioxide and water while using up oxygen (Bidwell, 1974).

Plants have anatomical, morphological, and physiological adaptations to allow the exchange of internal oxygen and carbon dioxide with gases in the atmosphere while conserving water to maintain a healthy water balance. Traits that modify these plant characteristics could affect photosynthesis, water efficiency, and irrigation practices.

Light provides the energy driving the photosynthetic process. During periods of inadequate light, plants cannot produce new carbohydrates and are forced to use stored carbohydrates to survive. When light is limited, such as when plants grow in shade, the plants that best exploit the available light may outcompete less efficient plants (Janick et al., 1981). Plants use both structural means, such as producing larger leaves or growing taller then their neighbors, and physiological means, such as producing more chlorophyll, to better utilize limited amounts of available light (Bidwell, 1974). Plant breeders exploit these adaptations to produce crop varieties that make the most of available light. Plants able to better exploit sunlight may grow successfully in environments previously unsuitable for crop production. In addition, a plant that uses light more efficiently may be grown at higher density (i.e., more plants per acre), thereby changing some crop-management practices.

(2) Physiological Environment

A plant's physiological environment, in general, refers to a plant's surroundings that influence its activities at a biochemical level—specifically, its ability to absorb, produce, and store nutrients and other substances.

Photosynthesis is a critical plant activity. It involves three processes: absorption and retention of energy from sunlight, conversion of light energy into chemical energy, and stabilization of chemical energy into stored energy in the plant (Bidwell, 1974). The process of photosynthesis can be accomplished in several subtly different ways. Variations in

photosynthetic processes have evolved that enable adaptation to specific environmental conditions, such as low light or restricted water. These adaptations may be biochemical or anatomical, resulting from one or more genetic changes in the plant. Although breeders have been trying to improve photosynthetic efficiency for many years, success has been limited for a variety of reasons (Richards, R.A., 2000). Alterations to photosynthetic efficiency may affect yields but increased yields may be dependant on additional water and fertilizer. Changes in photosynthetic efficiency may change overall environmental fitness which could affect both crops and wild plants bearing the traits.

Although they produce carbohydrates to be used as energy via photosynthesis, plants are still reliant on the soil as a source of mineral nutrition. Nitrogen, phosphorus, potassium, iron, magnesium, and other elements must be absorbed by plant roots and transported to tissues where they participate in myriad biochemical reactions necessary for plant survival and growth. For the most part, these minerals are either already present in the soil or have been added by a grower in the form of fertilizer. Plants rely on the fact that soil water dissolves the minerals and makes them available for uptake by the roots (Van der Have, 1979). It may be possible to produce plants through genetic engineering that are better able to take up minerals from the soil or that are able to use soil minerals more efficiently. Such traits could increase plant fitness and possibly alter crop management practices, specifically how much fertilizer a grower needs to use to achieve optimal yield.

Certain symbiotic soil micro-organisms associate with plant roots to increase nutrient availability. For example, *Rhizobium* bacteria associate with the roots of some plants, mostly legumes, take nitrogen from the air (which cannot be used directly by plants) and convert it into ammonium, which can be taken up by plant roots. Certain soil fungi, called mycorrhizal fungi, associate with plant roots making some soil nutrients, like phosphorus, more available for uptake (Brady, 1974). Breeders are interested in increasing the number of plant species able to associate with these micro-organisms, and other researchers are working with the micro-organisms themselves to improve their efficiency as nitrogen-fixing symbionts. Increasing the benefit obtained from symbiotic relationships with soil microbes, through genetic changes in either the microbe or the plant, may increase plant fitness, increase the geographic ranges of some crops and possibly lessen the amount of fertilizer growers need to apply or otherwise change soil fertility management practices.

In addition to carbohydrates, fats, and proteins made by plants for growth, plants also make a wide variety of additional substances called secondary metabolites. Secondary metabolites do not appear necessary for growth

but many have important functions in such areas as disease resistance, reproduction, and herbivory reduction (Verpoorte et al., 2002). Many of these substances are of interest to breeders, either because the secondary metabolite makes the plant more tolerant of environmental stress or because the metabolite is valuable to humans for pharmacological or other purposes. Altering secondary metabolite production may change environmental stress tolerance, or it may result in a plant with higher value as a crop because the metabolite itself is useful.

(3) Ecological Environment

In most environments where plants grow, one or more resources (e.g., light, water, nutrients, and space) are in limited supply, and plants growing together in the same location are generally competing with each other for the same resources. When the plants are a managed crop, the grower attempts to supply limited resources to the crop so that the individual plants are not competing with each other and are each growing at or near full potential (Janick et al., 1981). However, other plants growing with the crop can also benefit from the resources provided by the grower and take them from the crop. These plants are considered weeds and are removed when possible to reduce unnecessary competition and waste of resources intended for the crop. Breeders are always looking to develop crops that make more efficient use of resources to reduce competition and reduce inputs from the grower. In unmanaged environments, wild plants also compete for resources, but because no grower is supplementing their supply of resources, plants with more competitive adaptations and more efficient resource use may tend to grow better and reproduce more than their less competitive neighbors.

Two positive interactions between plants and other organisms, *Rhizobium* bacteria and mycorrhizal fungi, were discussed above. There are other examples of positive associations between plants and other organisms. Plants are pollinated by a variety of insects, birds, and mammals. Many animals assist plants by disseminating their fruits and seeds; still other animals, such as ladybugs, help plants by eating insect pests, like aphids. Other associations appear neutral, as far as the plant is concerned. In some cases, plants provide a beneficial habitat for the organism, for example, when a spider builds a web using a plant for support. Another kind of neutral association between plants and other organisms occurs after plants die. Dead plant material provides food to a wide variety of organisms from vertebrate and invertebrate animals to thousands of micro-organisms, which all feed on the plant debris until it is completely broken down. APHIS is unaware of research into GE traits altering these types of positive and neutral interactions between plants and other organisms; however, the agency anticipates that such traits, if developed, could affect

plant fitness and may also affect the associated organisms, as well as other organisms.

There are many associations between plants and other organisms in which the plant suffers some harm. The organism may eat the plant or feed from the plant. For example, caterpillars, aphids, and nematodes all get nutrition from plants at the plant's expense. Organisms such as bacteria, fungi, and viruses cause plant diseases that can either kill the plant or weaken it so that it cannot reproduce or compete with weeds. The organism may use the plant to launch an attack on other plants, as a means of completing its life cycle, or as a place to overwinter. Obviously, breeders care a great deal about minimizing the occurrence and intensity of these negative interactions and focus significant efforts to develop disease resistant crops (Fehr, 1987). Complicating the use of disease-resistant crops is the evolution of new strains of disease organisms that can overcome the plant's resistance. Disease and insect resistance derived by either genetic engineering or conventional breeding are traits with which APHIS is very familiar, and the agency anticipates continued interest in the development of these traits. Such traits could be expected to increase plant fitness, change crop-management practices (especially pesticide use) and potentially raise questions of impacts on nontarget organisms and development of resistance within pest populations.

In general, APHIS expects plant breeders to continue to improve crop performance and value using traditional breeding and GE traits. APHIS currently examines the potential impact of the trait on the health of the plant and on the environment with which the plant interacts.

b. Seed Biology and Commercial Seed Production

This section will look at the biological nature of seeds and will briefly describe how seeds are produced for commerce.

(1) The Role of Seeds

Seeds produced by plants have been the foundation of agricultural development by the human race for well over 10,000 years. During this time, humans have progressively transformed selected plant species from wild progenitors into highly specialized crops. Seeds are used as a source of energy and nourishment for human and animal consumption. They produce fibers used in clothing and construction. They are a source of raw materials for manufacturing an ever-broadening array of commercial products, and they are becoming an increasingly valuable source of renewable energy. The market value of agricultural seeds produced for planting each year is tens of billions of dollars worldwide. The world

production of major grains and oilseeds produced from seed is approximately 2.5 billion tons, worth more than $1/2 trillion.

(2) The Biology of Seeds

Seeds contain the genetic instructions passed down from their parents and serve as the conduits for transferring that genetic information to the next generation. Plants have developed a wide array of mechanisms to increase the chances of successfully passing genetic information on to the next generation.

Most crop plants reproduce sexually, which increases variation among the offspring and has advantages in natural evolution, but sexual reproduction requires a carefully orchestrated interaction between male and female gametes. Successful mechanisms involve variations in flower morphology, mechanisms of pollen dispersal, self-incompatibility (a mechanism to promote outcrossing), and sensitivity to environmental cues.

Knowledge of these reproductive strategies has enabled humans to transform wild progenitors into agronomically useful crops through many generations of crossing plants followed by the selection of desirable individuals in the progeny. These same reproductive strategies, however, can create challenges for maintaining genetic purity of seeds, particularly in crops that utilize natural environmental conditions to aid pollen and seed dispersal.

Although there are many physical variations, all plants produce flowers with the same basic anatomy. The stamen contains the male reproductive parts (anthers), which produce pollen. The pistil carries the stigma (the pollen receiving structure) and contains the female reproductive parts (ovules), which house the egg cells.

"Complete" flowers contain both male and female reproductive parts. Plants with perfect (complete) flowers are largely self-pollinated, although it is still possible for pollen from another plant to cause fertilization under certain conditions. This can have a significant impact on the genetics of a population.

The flowers of some plants require cross-pollination (i.e., pollination by another flower). Maize tassels, for example, produce flowers that do not usually develop female structures and produce only pollen. The flowers on the rachis (ear) do not develop male floral structures and require pollen from the tassel for pollination. This mechanism of separating male and female flower parts increases the probability of cross-pollination. The

flowers of some plant species (termed self-incompatible) cannot pollinate themselves, which maximizes mixing of genes between plants.

It is important to understand that most plants, including crop plants, fall somewhere in the middle of these extreme reproductive strategies. Self-crossing plants are rarely 100 percent self-fertilizing, and many cross-pollinating plants are not entirely self incompatible. This leads to a range of observed outcomes that must be considered when discussing plant reproduction.

(3) Pollen and Seed Dispersal

Forcing cross-pollination in crops with perfect self-pollinated flowers, such as soybean and wheat, requires that either pollen be inactivated or anthers be physically removed before they mature and release pollen. In either case, the pollen from another plant is delivered to the stigma.

In plants that are self-incompatible or have separate male and female flowers, pollen must be delivered to the female flowers by wind dispersal, animals, or, in most cases, insects. Corn pollination, for example, relies on wind dispersal of pollen. This reproductive strategy requires the corn plant to produce a large abundance of pollen that must travel through the air before landing on female flowers on the same or another plant.

Plants that rely on cross-pollination create challenges for those concerned with genetic purity: breeders, seed producers, grain growers, and sometimes consumers. For example, with few exceptions, the female flowers of corn will accept pollen from any corn plant. The seed industry continues to refine isolation standards and develop novel genetic, physical, and chemical mechanisms to minimize cross pollination (for corn, see Beck, 2004), and employs the latest pollen dispersal models to predict loss of genetic purity under field conditions (Fonseca et al., 2004).

(4) Seed Development, Maturation, and Long-term Viability

After fertilization, the developing seed becomes the primary recipient for water and photosynthetic products of the plant, rapidly gaining weight due to embryo development. The seed must store the chemicals that will be used to feed the growing seedling at the early stages of seed germination. The chemical composition of a seed is determined by genetic and environmental factors. Carbohydrates, fats and oils, and proteins are among the most important seed-stored compounds.

Wild plants must disperse their seeds into the environment in order to propagate and they have evolved a variety of mechanisms to accomplish

this. In general, humans have selected for crops that have reduced or entirely lost their ability to disperse seeds as part of the domestication process. This greatly improves the ability of farmers to collect the seeds for use as food or for propagating their crops. Still, many crops have not been fully domesticated and may retain some portion of their ancestral seed dispersal mechanisms. For example, in oilseed rape or canola the loss of grain prior to harvest represents a significant production problem. Even in crops that are highly domesticated, seeds retention is rarely perfect and seeds may be dispersed during the harvesting process. Mechanisms of seed dispersal are relevant to the discussion of gene flow into unmanaged environments.

After physiological maturity, the seeds of many species dehydrate, which helps seeds survive cold winters and dry periods. These seeds have the ability to dehydrate to very low moisture content while remaining viable, even though their moisture content is 8 percent to 12 percent (well below the 70 percent water that makes up all living tissues in plants). Not all seeds, however, will undergo dehydration: seeds from plants adapted to tropical environments usually do not dehydrate as much as those from temperate climates. At low temperatures and moisture content, seed metabolism diminishes and seed aging slows. Depending on seed composition, original seed quality, and storage conditions, seeds can be stored for several months to several years in an insect-free, low temperature, and dry environment. In some instances, seeds have been known to survive for 100 years or more.

(5) Accumulation of Storage Materials

Seeds, primarily cereals and legumes, make up 70 percent of the food consumed in the world. Seeds store large amounts of chemical substances such as proteins, carbohydrates, and lipids (fats and oils), in order to provide food to the seedling at the early stages of germination and growth.

Proteins are made primarily of amino acids. Enzymatic proteins catalyze biochemical reactions in plant cells. Some proteins make up structural components of cells and others are important stored food components of many seeds, especially legumes.

Carbohydrates are the most important storage compounds in the seeds of cereal crops. Starch and hemicellulose, the two main forms of carbohydrates stored in seeds, are the source of simple sugars needed for germination.

Lipids or fats serve as energy storage within the seed and are an important part of all cell membranes. Lipids are also used in food and animal feed

and in industrial applications. Fatty acids from seeds contain larger amounts of unsaturated fatty acids (those containing one or more double-bonds within their molecule) than lipids of animal origin, and these plant lipids are used increasingly in processed foods.

DNA is a natural component of all plant tissues, including seeds. The DNA content of the seed is vital because it provides the biochemical instructions for germination growth and development of the new plant. DNA is broken down during digestion when eaten, and its consumption in food, regardless of genetic information content, has no impact on human health.

(6) Opportunities for Genetic Modification

Nutritional studies also indicate that seeds are important sources of vitamins, antioxidants, and phytohormones. During the past 2 decades, there have been major advances in the understanding of biosynthetic processes controlling the synthesis and accumulation of these products in seeds. In concert with the development of molecular biological techniques, this knowledge has made it possible to modify seeds from crop plants to improve human health and produce raw materials for nonfood uses. Transforming seeds for these purposes may involve the addition of genes not currently present in the plant. Numerous studies to date indicate that seeds of some plants can be induced to synthesize and accumulate various novel compounds. For plants that will be produced in large scale such transformations need to be made with minimal effect on seed development, seed physical characteristics, and viability. It is likely the accumulation of normal seed storage components will need to be modified as well if seeds are to accumulate new compounds in sufficient quantity. A new genotype with poor agronomic characteristics and low capacity for seed production will not survive long in the seed industry.

(7) Commercial Seed Production

Before the 19th century, farmers generally saved seed for next year's planting, and seed commerce was limited to the replacement of stocks that had become mixed or degraded. The advent of modern plant-breeding methods has led to the importance of seed as a commercial product valued for its particular trait purity and quality components.

The increased sophistication of plant breeding to produce crops meeting very specialized needs and market niches has in recent decades increased the need for high standards of seed genetic purity in order to ensure identity preservation in increasingly diversified markets. In addition, the production practices associated with certification of seed have become an

important tool for controlling fungal, bacterial, and viral pathogens that depend on seed transmission for the spread of disease (Cook, R.J., 2000).

This section of the document describes in broad terms the two paths taken by commercial seed producers in developing and producing seed: traditional breeding and genetic engineering.

As background, these discussions are preceded with information concerning the trade and value of commercial seed. Additionally, to assist in understanding, basic information is included concerning plant pollination and a description of the differences between breeder seed, foundation seed, and certified seed during seed stock production.

Commercial Seed Trade and Value

Seeds are internationally traded commodities. The United States is the largest producer and consumer of seeds in the world. An estimated $5.7 billion worth of commercial seeds are produced annually in the United States, which has a 19-percent share of the $30-billion world seed market. Maize seed is the largest segment of the U.S. domestic-planting seed market valued at $2.2 billion. Annual U.S. seed exports and imports are estimated roughly at $800 million and $400 million, respectively, thus providing a net trade surplus. The United States exports seeds mainly to Mexico, Canada, Italy, Japan, and Argentina; imports come mainly from Canada, Chile, the Netherlands, and China.

In the United States, farmers purchase a large portion of seeds from commercial sources, and the commercial sector is engaged in production, conditioning, distribution, and marketing of seeds. Government policies and regulations impact interstate movement of seeds within the United States, and have an even greater effect on international seed commerce. These laws, policies, and regulations control plant variety protection, variety registration, truthful labeling, phytosanitary certification, and seed certification. Science-based policies and regulations are vital to the harmonization of the protocols for import and export among countries to promote global seed trade.

Self-pollinating Plants Versus Outcrossing Plants

For commercial seed producers, one of the principal seed quality concerns is genetic purity. To discuss genetic purity it is useful to divide plants into self-pollinated and outcrossing because genetic purity is linked to these modes of seed fertilization. Of course, all combinations of intermediates and some unusual cases exist.

It is simpler to produce seeds from self-pollinating plants than from outcrossing plants. Seed production of self-pollinated plants starts with the production of so-called breeder seed by self-pollination in research nurseries, followed by repeated cycles of seed production in plots that are checked for off-types. Self-pollinated plants are well-adapted for inbreeding and, as a result, are less likely to be used as commercial hybrids.

In outcrossing plants, the chain of breeding and production steps includes opportunities for both pollen flow and mixing. Insect pollination of outcrossing plants is common, and when it occurs it adds complexity to pollen control. It is much easier to produce hybrid varieties in outcrossing plants, and this makes the use of hybrids much more common in outcrossing crops than in self-pollinating ones.

Crop Improvement Through Traditional Breeding

Delivery of genetic improvements is one of the most important roles of the seed industry. Conventional breeding, at its most basic, is a process in which differences in plants are observed in small populations. The differences are compared with the needs of the person doing the selection for the best plants, and the plants that most fit the selector's needs are saved and perpetuated. Other variants are eliminated from selection. In modern plant breeding, breeders apply the principal of selecting favorable varieties using a range of modern methods including genetic, molecular biology, and statistical analysis.

Breeder Seed

Breeder seed is usually produced in research nurseries where individual plants can be inspected and where pollination control can be maintained. Intensive observation of individual plants allows high levels of purity to be maintained. The use of breeder seed keeps the seed system from accumulating unintended genes indefinitely over time. For some noncommercial and traditional landrace or heirloom varieties, there may not be an effective breeder's seed system.

Foundation and Certified Seed

Lower grades of seed are produced from breeder seed. Foundation seed is produced directly from breeder seed or other foundation seed under conditions designed to maintain specific genetic purity and identity of the seed. Certified seed is produced from breeder or foundation seed under conditions designed to maintain satisfactory genetic purity and identity. Certified seed is the highest grade of seed ordinarily planted by farmers.

For outcrossing plants, unintended crossing during open pollination is the major source of unintended ("off-type") pollinations in the field. Isolation and borders effectively limit the level of unintended off-types in the final product and their use is supported by decades of experience with plant breeders and the seed industry. Experimentation has shown that pollination of outcrossing plants declines rapidly with increasing distance from the source. The vast majority of unintended outcrosses and off-type plants come from adjacent fields, although rare, long-range crossing does occur. The advent of DNA-detection technology provides a sensitive means for monitoring gene transmission and has led to recent controversies over inadvertent trait occurrence which, in turn, has lead to tightening of production standards and practices for all seed-production systems. Regardless, for an open-pollinated plant, outcrossing at low frequencies will always be a possibility.

The other possible source for unintended presence of off-type genotypes in seed of both outcrossing and self-pollinated plants is commingling. Seed mixing during harvest, transport or storage tends to be a large source of impurities. In outcrossing plants, industry experience indicates that field contamination is a more frequent source of off-type genotypes than is mixing in planting, harvest, transport, and processing. However, careful application of the procedures for field production, transport, and processing of corn, for example, normally results in the production of both hybrid and self-pollinated seed that is at least 99 percent pure.

Technical Innovation and Seed

Breeding makes changes by combining great numbers of genes and sorting out useful changes by selecting among progeny. Genetic engineering selects a specific DNA sequence and makes it work in a new place. The changes made by genetic engineering are minor in comparison to the amount of DNA in the plant, typically 1 or 2 genes inserted among approximately 30,000. After a trait has been successfully incorporated, it can be added to other varieties of the same species by conventional breeding techniques.

The emergence of specialized food crops (e.g., zero trans fat crops) and nonfood varieties (pharmaceutical and industrial plants) increases the need to consider heightened standards for preventing pollen outflows and seed mixing in specialty seed production and brings up the special need to isolate nonfood varieties from food varieties.

The primary quality characteristics are physical purity, presence of other crop seeds and weed seeds (especially noxious weeds), germination, varietal purity, disease status, and moisture. Special germination tests for difficult conditions may add important information. However, the customer cannot readily observe the quality of purchased seed. Seed laws ensure that the seed merchant is providing accurate information. Both Federal and State governments have seed laws, and the International Seed Testing Association provides global standards for germination testing for international commerce. All official seed-certifying agencies belong to the Association of Official Seed Certifying Agencies (AOSCA), which establishes minimum standards for each crop. Individual certifying agencies may set higher standards than AOSCA, but not lower.

Many countries have customer-protection regulations that require varieties to meet performance standards. Varieties that meet the standards are described and registered and are then eligible for certification. The United States has few regulations of this type. Certification by the Organization for Economic Cooperation and Development provides international mutual recognition of certification. In the United States, both varieties and genes can be patented. Varieties can also be protected under plant breeder rights. The International Union for the Protection of New Varieties of Plants coordinates a simplified plant breeder's rights system with standardized claims.

c. The Future of Agricultural Plant Biotechnology

The first decade of commercial plant agricultural biotechnology has seen remarkable growth, from a mere 6 million acres in GE crops in 1996 to more than 220 million acres in 21 countries in the 2005 growing season. This represents between 4.5 and 6.3 percent of the world's total arable land. The year 2005 also marked the point where cumulatively more than 1 billion commercial acres of GE crops had been grown worldwide. This rapid growth has more recently slowed due to a combination of many complex market factors. This situation is further exacerbated by the fact that the vast majority of GE crop plants only carry two production-oriented traits—glyphosate herbicide resistance and insect resistance, and some regional markets for these two traits may be reaching near saturation.

Notwithstanding these concerns, continued worldwide expansion in the use of GE plants is likely. This is exemplified by the activities of government regulators around the globe who are working to create regulatory regimes which allow GE plants and plant products to reach the

marketplace while assuring that the products are safe for people and the environment. Concomitant with this governmental activity, the academic, nonprofit, and corporate communities are working on creating new identity preservation, quality and trait assurance programs, and market-channeling mechanisms to allow GE plant products to flow in commerce without the inadvertent contamination of other products.

Looking to the future, there are four areas of GE crop trait developments that may experience rapid growth and significant worldwide commercialization in the next decade. These developing crop traits would focus on efforts to address environmental stress on plants, and to produce plant-derived biofuels, plant-produced proteins, and substances with industrial applications.

Due to a decreasing supply of high-quality crop production land, drought, desertification, salinization, and global warming, there is a critical need for culturally acceptable food, fiber, and feed plants that can flourish under these environmental stresses. There is a broad scientific effort to identify and introduce traits that will allow plants to deal with these environmental stresses, especially for use in developing nations.

With the rapid escalation in petroleum and fossil-fuel prices, significant scientific effort is being expended to develop renewable plant-derived fuels. The most interesting GE plant-derived biofuels from an intermediate-term development period of 10 to 15 years are ones that may be grown, extracted, and utilized without further modification or with limited modification, much like existing biodiesel products. Members of the plant kingdom are capable of synthesizing an extremely wide variety of chemical substances and are fully capable of producing large, complex proteins in useful quantities.

The next 10 years will see an increase in the development of GE plant-derived protein products such as vaccines, enzymes, biologicals, and new, custom-designed, therapeutic proteins to treat cancer, birth defects, and chronic ailments.

The fourth area that seems destined for increased development and commercialization in the next decade is nontraditional industrial chemicals such as adhesives, improved or unique plant-derived fiber, lubricants, pharmaceuticals, nutritional supplements, and food-derived health supplements.

2. Assessing Effects on the Human Environment

To understand how APHIS' current biotechnology regulations and possible changes to them might impact the quality of the human environment, it is important to understand the basic principles and approach for conducting risk assessments of GE organisms.

To begin, this section gives a general introduction to how potential effects of GE organisms on the human environment are typically assessed.

Section A.3, which immediately follows, discusses several issues of potential impacts that have been and will continue to be considered in completing risk assessments for specific GE organisms.

Section A.4 then discusses several examples of GE modifications for specific plant qualities and elaborates on the risk assessment issues associated with them. Among other modifications, this subsection provides information concerning GE insect-resistant crop plants modified to express genes from *Bacillus thuringiensis* (Bt).

As a reminder, it is critical to note that the particular regulatory action and decision required determines the type of risk assessment performed as well as the specific NEPA environmental documents that are prepared. Moreover, both the risk assessments and the NEPA documents are always prepared on a case-by-case basis. The specific regulatory action and decision required will dictate which NEPA environmental document will be prepared (i.e., a categorical exclusion, an environmental assessment, or an EIS). We emphasize that this DEIS does not contain risk assessments for specific organisms since those assessments are done on a case-by-case basis. The purpose of this DEIS is to analyze the environmental impacts on the human environment resulting from APHIS' current regulations for GE organisms as well as to analyze the potential environmental impacts, if any, on the human environment resulting from any revisions or changes to APHIS' current regulations for GE organisms. Project-specific analyses and documentation on proposed actions performed under the regulations, such as permit applications and deregulation decisions, may be prepared on individual project levels, and public involvement will be solicited in accordance with the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures. These analyses will be tiered to this DEIS and other applicable EISs.

Since the advent of biotechnological methods, a wealth of experience with risk assessment has been accumulated worldwide, resulting in a robust international consensus on the general principles and methodology for risk

assessments regarding GE organisms. The overall methodology for risk assessment typically follows a number of steps:

1. *Hazard identification*—An identification of any novel genotypic and phenotypic characteristics associated with the GE organism that may have adverse effects in the potential receiving environment;

2. *Likelihood estimation*—An evaluation of the likelihood of these adverse effects being realized, taking into account the level and kind of exposure of the likely potential receiving environment to the GE organism;

3. *Consequence evaluation*—An evaluation of the consequences should these adverse effects be realized;

4. *Overall risk estimation*—An estimation of the overall risk posed by the GE organism based on the evaluation of the likelihood and consequences of the identified adverse effects being realized; and

5. *Risk management*—A recommendation as to whether or not the overall risks are acceptable or manageable, including, where necessary, identification of strategies to manage these risks, including monitoring.

In the process of conducting the steps outlined above, a risk assessment takes into account the relevant characteristics of the recipient organism, host organism, or parental organisms; the inserted genes and sequences and related information about the donor(s) and the transformation system; the resulting GE organism; the detection and identification of the GE organism; the organism's intended use (e.g., the scale of the activity—field test or commercial use); and the likely receiving environment.

3. General Topics Relevant to Risk Assessments

For the purposes of further describing risk assessments for GE organisms, this subsection discusses several issue areas of potential impact that have been and will continue to be considered in completing risk assessments for specific organisms.

The issue areas discussed below are: potential changes in weediness and invasiveness; potential effects of GE plants on soil; and potential impacts of GE plants on human health.

a. Potential Changes in Weediness and Invasiveness

A key consideration in assessing the potential risks of GE plants is whether or not changes in weediness or invasiveness have occurred or are likely to occur as a result of the genetic modification.

(1) Crop Plants and Weediness

Plants can evolve into weeds in three basic ways: (1) wild plants can, through unintentional selection in managed settings, gain the ability to invade managed habitats; (2) genes can be exchanged between cultivated crops and wild (noncultivated) relatives such that the wild relatives become weeds; and (3) weedy traits can be selected in crop plants such that the crop itself becomes a weed. It has been suggested that certain traits introduced through genetic engineering of crop plants might confer weedy characteristics to the plants, thereby, creating new weeds in managed areas. However, it is unlikely that new weeds or invasive plants would be created in this way (Martinez-Ghersa, 2003).

There are many common definitions of a weed, but most involve not a specific biological feature but rather how weeds are regarded by people (Booth, Murphy, and Swanton, 2003; King, 1966). The term "weed" is commonly defined as a plant growing where it is not wanted, due to its interference with human activities or human welfare (Anderson, 1977). For the purposes of this DEIS, the weediness of GE plants and wild relatives with acquired GE traits in agroecosystems and other areas managed by humans will be discussed separately from the invasiveness of these plants into unmanaged ecosystems.

There are also several common definitions of "invasive species" in the scientific literature (Richardson et al., 2000; Colautti and MacIsaac, 2004; Pyšek et al., 2004). In this DEIS, an invasive species is defined as an introduced species that has a substantial or transformative impact in the unmanaged environment.

All crop plants can be considered weeds when they persist as volunteers growing from seed left in a field after harvest. However, some plants have more weedy characteristics than others. Using common definitions such as the one given above, it is not possible to know whether any plant, GE or not, will be considered a weed in some particular instance. APHIS approaches this dilemma by comparing the biology of the GE plant to its nonengineered counterpart, usually the same plant without the GE trait.[15] In this way, conclusions can be drawn as to whether a GE plant is different than its nonengineered counterpart in its basic phenotypic characteristics and life history. It may be difficult to predict, based on phenotype, whether or not a GE plant would become a weed, but any significant change in environmental fitness might trigger the need for heightened

[15] APHIS has developed and made available on the Internet, http://www.aphis.usda.gov/brs/international_coord.html, a list of biological characteristics that petitioners for nonregulated status should address in their data set. The list is found in appendix II of the Canada/U.S. 2001 Bilateral Agreement on Agricultural Biotechnology.

scrutiny. To date, the incorporation of GE traits in crop plants has not resulted in the creation of novel weeds.

(2) Wild Relatives With Acquired Genetically Engineered Traits As Weeds

Many of the concepts and proposed mechanisms by which transgenes might increase the fitness and consequently, the weediness of plants would also apply to their wild relatives (Jenczewski, Ronfort, and Chèvre, 2003). An important difference, however, is that crop plants often are themselves not very weedy and have a low propensity for persistence when not managed in an agricultural context. In contrast, wild relatives, by their nature, may have weedy characteristics and an ability to persist in the environment. Hybridization of many species of traditional crop plants with their wild relatives is well established, and it is believed that the resultant gene flow may contribute to the evolution of weediness (Ellstrand, Prentice, and Hancock, 1999), but such instances are rare (Martinez-Ghersa, 2003).

In classic studies on the origin and evolution of weeds, Baker (1965, 1974) listed characteristics typically associated with weedy plants. The following is that list as adapted by Rissler and Mellon (1996):

1. Seeds germinate in many environments.

2. Seeds remain viable a long time.

3. Plants grow rapidly through vegetative phase to flowering.

4. Plants produce seeds continuously as long as the growing season permits.

5. Flowers are self-compatible but not obligatorily self-pollinated.

6. Pollen from flowers that are cross-pollinated is carried by nonspecialized flower visitors (usually insects) or by wind.

7. Plants produce large numbers of seeds in favorable environmental circumstances.

8. Plants produce seeds in a wide range of environmental circumstances.

9. Plants are adapted for both long-distance and short-distance dispersal.

10. If perennials, the plants have vigorous vegetative reproduction or regeneration from fragments.

11. If perennials, the plants readily break near the soil line to prevent easy withdrawal from the soil.

12. Plants compete by special means such as forming rosettes, choking growth, or producing toxic chemicals.

Keeler (1985) reviewed the evolution of weeds from crop plants focusing on the characteristics described by Baker that may distinguish weeds. She listed characteristics associated with weediness in certain species and noted that many of these characteristics are known to be controlled by single genes. Her work showed uneven distribution of such characteristics among crops, weeds, and other plants. While the most serious weeds had an average of 10 or 12 weedy characteristics, other randomly surveyed plants averaged 7, and crop plants averaged only 5. Thus, it seemed unlikely that most crops would acquire enough of these characteristics to become weedy, even if the traits could be inherited as single loci. While noting several limitations to her study, she concluded that GE crops with low weediness and no weedy relatives are no more likely to be the source of significant weed populations than their nonengineered counterparts.

However, Williamson, studying invasiveness, concluded that neither those traits listed by Baker, nor any others, can accurately predict which plants could become weeds (Williamson, 1993). He proposed, rather, that any such list of characteristics would have to be specific for groups of closely related species and noted that small genetic changes can sometimes spur large ecological changes. He concluded that GE plants have the potential to become weeds because the genetic changes may have unexpected environmental effects; however, he also concluded that the proportion of GE plants that will become weeds is very small (Williamson, 1993). This conclusion was based on an earlier study of invasive species which had led to his formulation of the "10:10 rule." According to this rule, approximately 10 percent of introduced species will become established and truly naturalized, and 10 percent of those will become pest species. Hence, for introduced species, as a rough estimate, only 1 percent will become pest plants. This rule could be applied equally well, and with equal validity, to traits that have been introduced using conventional breeding, such as pest resistance, or those which can be acquired naturally or introduced through conventional breeding efforts, such as herbicide resistance.

It has been suggested that the release of organisms with novel phenotypes bears similarities to the introduction of nonnative species (Marvier, 2001).

However, the usefulness of such a model for evaluating the risks of GE crops has been questioned (Hancock and Hokanson, 2001). The argument against exotic plant species as a useful analogy is that many of them are already good colonizers in their native habitats and carry an array of traits associated with weediness. Thus, when they are introduced into a new environment where there are few or none of the factors which may have limited their numbers in their native environment, populations can sometimes explode to fill an ecological niche.

There are examples of nonnative plants, such as field bindweed, quackgrass, and Canada thistle in heavily managed habitats, and kudzu, purple loosestrife, and cheatgrass in less-managed or unmanaged habitats, becoming weeds and causing significant impact to the environment, resulting in huge economic costs. This is in contrast to the antecedents of most GE crops, which are generally poor colonizers outside of the agroecosystem designed for their cultivation.

The traits selected for domestication and the ongoing development of most crop plants typically have made them less fit than their undomesticated counterparts in situations where the crop plants are not managed (Gepts, 2004). Although there are exceptions, as discussed above, crop plants generally have relatively few weediness traits. Thus, there are multiple and complex constraints that limit the weediness and invasiveness of typical agronomic crops and in most cases, only one such constraint would be removed by the addition of a single gene through genetic engineering. Hancock and Hokanson (2001) concluded that the risk of deploying GE plants can be effectively determined by considering the phenotype conferred by the transgene and the invasiveness of the antecedent crop.

Crawley et al. (2001) performed one of the few studies of GE plants where potential weediness and invasiveness were measured directly. This was done by monitoring different habitats for 10 years following the cultivation of four different GE crops, namely herbicide-tolerant sugar beet, maize, and rape, and potato producing either a Bt toxin or pea lectin. In none of the cases did the researchers find the GE crops to have increased fitness over that of the conventional controls, and no unintended effects for the particular crops were identified. The most important factor to consider in interpreting these results, however, is that the particular traits studied would not be expected to increase fitness, except for the Bt toxin under certain conditions. The authors noted that the results might be different for other types of traits, such as drought tolerance or certain pest resistance genes that might confer a fitness advantage under field conditions.

Pest resistance genes have been the focus of much attention in regards to plant fitness. Virginia Polytechnic Institute and State University's Information Systems for Biotechnology, with support from USDA, sponsored a workshop on "The Ecological Effects of Pest Resistance Genes in Managed Ecosystems" (Traynor and Westwood, 1999). Many participants felt that the types of pest-resistance traits being tested or released commercially were not fundamentally different from those introduced through conventional breeding and as such, would present similar ecological risks. However, some participants disagreed and contended that some transgenes could have a much greater impact on weediness. Most participants agreed that gene stacking (i.e., insertion of multiple transgenes) to confer a broad spectrum of pest resistance would be less predictable, with respect to ecological consequences, than single-trait resistance.

Snow et al. (2003) reported field studies of wild sunflower populations carrying a Bt *cry1Ac* transgene acquired via experimental hybridization to a noncommercial GE crop line and backcrossed into the wild-type plants. The Snow team observed decreased insect pest damage and increased fecundity (seed production) for the experimental unmanaged populations carrying the transgene versus those without it. This observation suggests the possibility that, by conferring increased fitness, the transgene could have an ecological impact on wild sunflower populations, by increasing the number of modified plants within a population, by creating more such populations, or by creating more extensive seed banks of such plants.

(3) GE Crops and Invasiveness

In addition to the development of weediness, there is concern that GE crops may escape cultivation and persist to a significant degree in unmanaged ecosystems. It is also conceivable that a transgene from a GE crop could be transferred via cross-pollination to a wild relative of the crop, producing hybrid offspring containing the transgene that could themselves persist in the environment, or through introgression (by repeated natural backcrossing), resulting in the incorporation of the transgene in the genome of the wild relative.

(4) Gene Flow via Escape of GE Crops

For a GE crop to become established in an unmanaged habitat, seeds or other propagative structures must be transported from cultivated land to the habitat. This can occur via seed spillage during the movement of harvesting equipment between cultivated fields or during the transport of harvested seed, or seed can be moved by animal activity, wind, or water. The abandonment of farms or fields is another potential method of GE

crops being introduced to an unmanaged environment, but only for deregulated GE crops.[16] Nonseed propagative plant material, such as stolons or rhizomes, could be moved via mowing equipment or by animal activity, wind, or water. However, the movement of seeds or other structures is independent of any transgenes in the crop genomes with which APHIS is familiar, so the escape of a GE crop is not inherently more likely than the escape of any other crop (Keeler, 1985). Although it is conceivable that transgenes increasing seed-dispersal rates could be engineered into crop plants, it is highly unlikely that this would be done. A primary goal for crop variety development is the prevention of seed loss via seed dispersal mechanisms (Frary and Doğanlar, 2003) because the seed or fruit is usually the plant part with the highest value. However, if seed-dispersal genes were to be altered in a crop plant, the resulting GE plants would merit increased scrutiny to verify that gene flow was not increased in ways causing significant environmental effects.

(5) Gene Flow Via Hybridization With Wild Relatives

The exchange of genes between crop plants and sexually compatible wild plants has occurred ever since plants were first domesticated. It is possible that a transgene could be established in the genome of a wild relative of the GE crop as a result of an initial hybridization between a GE crop and its wild relative, followed by introgression of the transgene into the wild relative's genome (Gealy, Mitten, and Rutger, 2003; Halfhill et al., 2004; Légère, 2005; Pilson and Prendeville, 2004). For a transgene to become incorporated in a wild crop relative, crop pollen carrying the gene would first need to be carried via wind or insects or other pollinators to a plant present in the crop field as a weed or present in a nearby unmanaged habitat. Conversely, pollen from a wild crop relative in the unmanaged habitat could be carried via wind or insects or other pollinators to a crop plant growing in a cultivated field. Hybrid seed produced in the crop field would have to be harvested along with the crop and be spilled onto noncultivated land, as discussed above, or dispersed by an animal, whereas, the movement of crop pollen onto uncultivated land could result in the production of hybrids with no seed movement necessary.

Hybridization between a GE crop and a wild relative is dependent on several key factors: simultaneous flowering, sexual compatibility, and proximity sufficiently close to allow pollen movement between the two plants. The first two factors are determined by the specific crop and wild relative, and can result in little or no outcrossing, as in the case of wheat, or frequent outcrossing, as in the case of rice, (Ellstrand, Prentice, and

[16] Under the terms of APHIS permits, fields planted with regulated GE plants may not be abandoned until it is established that there is no potential for any GE plants to volunteer in subsequent growing seasons.

Hancock, 1999). However, even when a crop can hybridize with a wild relative, the plants must be close enough together to allow pollination to occur. Again, this factor is different for every crop plant and depends on a variety of characteristics (including whether the crop is pollinated by wind, insects, or other pollinators), to what extent the crop is self-pollinated, how long-lived the pollen is, and how the crop is cultivated. However, these parameters have been studied in-depth in many agronomically important crops, and the Association of Official Seed Certifying Agencies has established standard growing conditions for crop seed production in many crops which result in very low levels of outcrossing (AOSCA, 2003).

(6) Invasiveness Potential

Only a small fraction of introduced species become successfully invasive (Ellstrand and Schierenbeck, 2000), and there is no evidence that crops improved via genetic engineering are more likely than conventional crops to be invasive. The potential for a GE crop or a GE crop/wild-relative hybrid to become invasive depends, first, on the ability of the plant to become established in the environment and second, on its ability to successfully persist and thrive. Very few crops have been shown to be persistent and invasive outside of cultivation (Hancock and Hokanson, 2001).[17] Initial establishment of a crop plant will depend on the crop's ability to survive without any human intervention. This includes successfully competing with other plants for nutrients, water, pollinators, and sunlight; surviving attacks by diseases, insects, and other herbivores; and producing sufficient progeny or propagative structures to maintain its presence in the environment (Brown and Mitchell, 2001; Ellstrand and Schierenbeck 2000; Mitchell and Power, 2003). The particular transgene introduced into the crop may also have some effect on the plant's survival. Because the weediness and invasiveness of a particular crop is known throughout the U.S. range where the crop is produced, the invasiveness of a GE crop possessing one or more transgenes can be estimated by evaluating the environmental fitness impacts of the individual introduced genes (Hancock and Hokanson, 2001).

In the case of GE crop/wild hybrids, establishment will depend on the fertility and overall vigor of the hybrid plants and their progeny (Vacher et al., 2004) as well as on the nature of the transgene. For example, naturally occurring hybrids between wheat and its distant relative jointed goatgrass are occasionally found, but the hybrids are usually self-sterile

[17] Crops considered to be persistent and sometimes invasive include barley, rapeseed, rice, sorghum, sunflower, and wheat. Crops considered to be persistent but not invasive include apple, asparagus, blueberry, cranberry, pear, poplar, spruce, and strawberry (Hancock and Hokanson, 2001).

due to a lack of proper chromosome pairing (Guadagnuolo, Savova-Bianchi, and Felber, 2001; Morrison et al., 2002; Seefeldt et al., 1998). However, it is also possible for interspecific and intergeneric crosses to exhibit enhanced fitness through heterosis, an increase of genetic diversity caused by hybridization (Vacher et al., 2004). A hybrid may possess a novel combination of traits, making it more able to adapt to an ecological niche than either of the parents (Ellstrand and Schierenbeck, 2000). In other words, each type of hybrid may exhibit unique and possibly unexpected characteristics. For example, hybrids between oilseed rape and wild radish are more fit when wild radish is the maternal parent (Gueritaine et al., 2002). But even so, fitness is very low and dependent on the particular environmental circumstances (Al Mouemar and Darmency, 2004; (Gueritaine et al., 2002). Fortunately, years of experience with cultivation and plant breeding have resulted in an extensive and growing body of information regarding the likelihood of hybridization between crops and their wild relatives and the fitness and fertility of these hybrids (Arriola, 1997; Stewart, Halfhill, and Warwick, 2003).

(7) Persistence of GE Crops in Natural Environments

The likelihood for a GE plant to persist in the environment depends primarily on the plant species and on the ecosystem in question, including competing species, diseases and herbivorous pests, and the physical environment. One factor that can be analyzed experimentally is whether the GE version of a crop plant has better field performance, that is, is more fit, or persists longer than a conventionally bred version of the crop. A recent study asked this question using GE and conventional varieties of corn, oilseed rape, sugar beet, and potato growing for 10 years in 12 natural habitats in Britain. The transgenes studied were for herbicide resistance, Bt toxin, and pea lectin (Crawley et al., 2001). The study found that none of the GE crops were more fit or persisted longer in the environment than the conventional crop counterparts. Establishment of seedlings of the herbicide-resistant corn and rapeseed was significantly lower than for the conventional versions of the crops, and survival of the GE potato lagged behind that of conventional potato (Crawley et al., 2001). However, it must be noted that none of the transgenes at issue in the study were intended to increase plant fitness in natural habitats.

There is little evidence that beneficial agronomic traits moved into crops via conventional breeding have led to the development of invasiveness in crop plants (Duvick, 1999). Similarly, it is unlikely that the mere entry of a GE crop plant into an unmanaged ecosystem will result in the permanent establishment of the plant in that ecosystem. To evaluate the environmental impact of a GE crop, researchers begin with the body of

knowledge developed through years of cultivating the non-GE version of the crop, including any information about its weedy or feral tendencies. It is then possible to superimpose any effects of the transgene on the already familiar traits of the non-GE crop (Parker and Kareiva, 1996). A systematic experimental approach, where the field performance of a GE crop and its non-GE counterpart are thoroughly compared in the greenhouse and in the field, should indicate whether the transgene has any unexpected effects on characteristics that could contribute to invasiveness (Wang et al., 2003).

The transgene may or may not confer any advantage to the GE plant, depending on the nature of the gene, the ecosystem, and the presence of human intervention or other factors that may provide sporadic or continuously acting selection pressure such as herbicide application, insect or disease attack, or environmental stress. Without this pressure, the transgene's effects would not be expected to manifest themselves, and the GE plant would be expected to be phenotypically indistinguishable from its non-GE counterparts in that particular environment (Vacher et al., 2004). For example, a transgene conferring herbicide tolerance would not increase fitness for the recipient plant unless the natural habitat was regularly treated with the appropriate herbicide (Pilson and Prendeville, 2004; Metz, Stiekema, and Nap, 1998). Lacking such management, the GE plants would not be expected to be any more fit than conventional plants of the same species (Pilson and Prendeville, 2004; Gueritaine et al., 2002). If, however, regular herbicide applications were used, the GE individuals could have a significant advantage over their non-GE counterparts. However, not every transgene would be expected to respond to selection pressure. For example, a crop containing a transgene that alters a food-quality trait is unlikely to have any effect on plant fitness because there is unlikely to be a corresponding selection pressure for the trait (Parker and Kareiva, 1996).

If the transgene confers insect or disease resistance, the recipient plant may gain a fitness advantage, but only if the insect pest or disease organism ordinarily acts to control the normal distribution or role of that plant in that particular environment (Parker and Kareiva, 1996). In that case, it would be expected for the GE plant, whether crop or wild-relative hybrid, to have a fitness advantage over other plants in the environment (Vacher et al., 2004). The greater the impact of the insect pest or disease on the vigor and reproductive potential of the plant population, the more likely it is for the GE plant to have a fitness advantage over non-GE counterparts (Parker and Kareiva, 1996). Over the course of many generations, with continuous selection pressure from the insect pest or disease, the GE plant could become invasive, in the case of a crop plant, or could replace the non-GE population, in the case of a GE wild relative.

If the transgene in question confers an agronomic characteristic, such as drought tolerance or increased photosynthetic efficiency, the recipient plant could become invasive or replace its non-GE counterpart but only if a corresponding environmental stress consistently acts to control the plant populations in that ecosystem (Pilson and Prendeville, 2004).

APHIS anticipates that as plant genetic-engineering technology advances, applicants will propose, with greater frequency, field tests of plants with traits such as increased photosynthetic efficiency and tolerance to various environmental stresses. Such traits, either singly or in combination, could contribute to the invasiveness of a GE crop, or GE crop/wild-relative hybrid, or introgressed progeny. However, given that most crop plants are not naturally invasive and that most cultivated crops possess several domestication traits (Frary and Doğanlar, 2003; Gepts, 2002), such as dwarfing, nonshattering seed heads, and larger fruits, which usually are disadvantageous in unmanaged ecosystems, it has been proposed that a single plant would have to possess several transgenes conferring improved fitness characteristics before it would become invasive (Hancock and Hokanson, 2001). The insertion of multiple genes affecting fitness in a single plant, so-called stacking, is more likely as genetic engineering technology advances, and plants with such gene stacks would receive additional scrutiny to determine their potential for weediness or invasiveness.

A single instance of gene flow to an unmanaged ecosystem or a transgene into a wild relative may not result in the development of an invasive population of GE plants (Ellstrand and Schierenbeck, 2000; Siemann and Rogers, 2001). Even if the initial introduction succeeds, a lag time of several generations may be necessary during which time the introduced species may undergo genetic adaptation, ultimately making the plants better able to survive in their new environment than other species or non-GE populations of the same species (Siemann and Rogers, 2001; Willis, Memmott, and Forrester, 2000). Multiple introductions via repeated instances of gene flow may be necessary before a potentially invasive species can become established (Pilson and Prendeville, 2004; Ellstrand and Schierenbeck, 2000). Delays in the development of invasiveness may also depend on the crop or crop relative in question (Ellstrand and Schierenbeck, 2000). For example, trees, shrubs, and other perennial plants with long reproductive cycles may take decades or longer to develop invasiveness, assuming no human intervention, while annual plants or short-lived perennials may become invasive only a few years after an inadvertent instance of gene flow (Ellstrand and Schierenbeck, 2000). Minimizing the size and frequency of transgene flow to unmanaged ecosystems is, therefore, the most direct way to minimize the

development of invasiveness both in the short term and over long lag periods.

b. Potential Effects of GE Plants on Soil

In assessing the potential risks of GE plants, another key consideration is whether or not modified organisms will alter or impact the soil environment.

Plants and the soil and water environments in which they reside are inarguably intertwined. The plant-soil matrix is a complex environment of interactions between abiotic and biotic components. These interactions can be considered on both a small and large scale.

On the small scale, seeds germinate within the soil; the resulting seedlings and plants interact with the soil and also the micro-organisms and water within it to obtain nutrients. The nutrients fuel vital functions, such as growth and reproduction. The soil is then enriched through plant decomposition by scavengers and other soil-dwelling organisms.

Interactions also exist on a large scale. Traditional agricultural practices, including tillage, irrigation, and herbicide and pesticide use have significant and predominately detrimental environmental impacts (Ammann, 2005). Both scales of interactions should be considered when evaluating the potential effects of GE plants on soil and water environments.

Soil is a highly dynamic environment. A single gram of soil typically contains millions of individual organisms, including several thousand species of bacteria alone (Torsvik et al., 1994). These organisms enable decomposition, which leads to soil formation, aeration, and nitrogen fixation, and aid in root function (Giller et al., 1997). The immense number of organisms and the complicated and poorly understood relationships between these organisms, the environment, and plants complicate the analysis of the potential effects of introducing GE plants and other organisms (Lilley et al., 2006).

The text that follows discusses the factors that are considered when evaluating the potential effects of particular genes on the soil and groundwater environments.

(1) Accumulation and Persistence

Some traits added to plants via genetic engineering involve the production of one or more substances that the plant would normally not produce.

Novel chemical substances produced by GE plants may enter the environment from leaf shedding, root exudates, and decomposition (Donegan et al., 1997). If these substances do not dissipate at a rate at least equal to the rate of the products' entry to the soil system, bioaccumulation and biomagnification may result. Bioaccumulation is the increase in concentrations of chemicals in biological systems over time as compared to the chemical's concentration in the environment. This occurs when a chemical becomes more and more concentrated as it moves up the food chain.

Additionally, herbivorous animals that feed on these plants and subsequently die, either due to natural causes or due to consuming a pesticidal substance such as a Bt toxin, may also add these novel chemical substances to the soil environment. The substances in the plant may not necessarily be in the same form in the insect. For example, the Bt protoxins made by insect-resistant GE plants are modified in the guts of susceptible insects (Höfte and Whiteley, 1989).

Bt crops offer the best-studied example to date of accumulation, persistence, and residual toxicity within the soil (Clark et al., 2005; Höfte and Whiteley, 1989; Saxena et al., 1999). For example, studies have compared the decomposition rates of Bt and non-Bt crop residues, although with inconsistent results (Cortet, 2006; Stotzky, 2004). The binding of chemical substances by soil particles is also a factor. The Bt toxins adsorb and bind rapidly (< 30 minutes) to clays and organic matter within the soil, allowing the Bt toxins to persist and also to remain toxic to insect larvae (Stotzky, 2000, 2002). In nonflooded soils, the Bt toxins released from root exudates and biomass of Bt corn were bound to soil particles and remained larvicidal for at least 180 days (Tapp and Stotzky, 1998), and toxins remained detectable in the biomass of Bt corn 3 years after incorporation into soil (Saxena and Stotzky, 2003). The Bt endotoxin associated with Bt crops appears to degrade rapidly in water, with a half-life between 4 and 10 days, depending on the presence of micro-organisms (Douville et al., 2005). This result suggests that the persistence of Bt toxin in water bodies adjacent to land planted with Bt-engineered crops is not a significant concern; however, more studies need to be done to further evaluate persistence in soil and sediments in water bodies. Obviously, soil and natural bodies of water are not sterile environments, and many abiotic and biotic factors will affect persistence such as soil type, aeration, water movement, and soil biota activity.

GE plants may add more than novel chemical substances into the soil. DNA is also released into the soil as organisms decompose. Clay minerals bind DNA molecules and can prevent vertical movement of DNA within the soil and thus, delay DNA degradation by protecting free DNA from

degradation (Greaves and Wilson, 1970). The presence of DNase in the soil can also affect the accumulation and persistence of DNA in soil (Blum, Lorenz, and Wackernagel, 1997; and Dunfield and Germida, 2004). Studies so far have demonstrated persistence of GE DNA in soil from several days (Widmer et al., 1997) to at least 2 years (Gebhard and Smalla, 1999). The impacts of DNA in the soil are discussed later in this section.

Biomagnification and bioaccumulation of products released by GE organisms should be considered and compared with similar, potentially cumulative effects from traditional crops (Sanvido et al., 2006). APHIS is unaware of any studies or data demonstrating bioaccumulation or biomagnification as a result of planting GE plants. In cases where, biomagnification and bioaccumulation are likely, expression of transgenes in GE organisms can be manipulated in ways that may mitigate those undesirable phenomena. For example, new techniques that limit the expression to specific plant parts rather than the whole plant or prevent expression except in the presence of specific environmental stimuli can significantly limit how much of these products enter the soil.

(2) Water and Movement Away From the Site

Water can move products from GE organisms away from the immediate site of entry into the soil environment. Precipitation, runoff, and irrigation will provide transport for these products through the soil column. These products can enter groundwater, where they may be transported to larger underground reservoirs used for drinking water, or to neighboring streams via underground conduits. Soil factors affecting how water will move GE products include, but are not limited to, soil type, texture, permeability, and the depth of the water table.

Besides interactions on the small scale (e.g., increasing the number of organisms that are exposed as products of GE crops are carried by water out of the rhizosphere), there are large-scale impacts that should be considered. For example, currently available GE glufosinate- and glyphosate-tolerant crops allow farmers to replace triazine and chloroacetanilide herbicides with less toxic and less environmentally damaging glufosinate- and glyphosate-based herbicides. These herbicides are readily degraded by soil-dwelling bacteria and fungi. Accordingly, they have a lower potential to reach water resources, leading to reduced risk of drinking water contamination and improvements in the water quality of vulnerable watersheds (Wauchope et al., 2001).

(3) Interactions With Soil Organisms

Soil- and plant-associated microbial communities and their interactions are not well understood, and modern agricultural cropping systems can affect these interactions (Dunfield and Germida, 2004). Soil communities are incredibly diverse and include beetles, springtails, mites, worms, spiders, nematodes, fungi, bacteria, and other organisms. Only a small portion of species within the classes of soil organisms have been described. For example, as many as 35,000 soil-dwelling fungi have been identified, while the projected number is greater than 100,000 (Hawksworth, 1991). These organisms improve the entry and storage of water, soil mixing, resistance to erosion, plant nutrition, and breakdown of organic matter (Giller et al., 1997).

Plants develop mutually beneficial relationships with soil organisms in the rhizosphere, and these relationships are heavily affected by metabolites released by plants into the soil. Root exudates have been proposed to be the most important factor in the development of the rhizosphere microflora (Lynch and Whipps, 1991). Genetic modifications in plants may alter these root exudates and affect the associated microflora (Pilson and Prendeville, 2004). The incorporation of plant residues into the soil may affect organisms that are not directly associated in a mutualistic relationship with the plant but serve indirectly beneficial functions (e.g., scavengers and decomposers), or that protect plants from detrimental micro-organisms (Bashan and Holguin, 1998). The degree to which these effects result in measurable changes to soil ecosystems may be difficult to assess. Additionally, the origin of the transgene should be considered. For example, soil-dwelling organisms are likely to have had previous exposure to proteins from *Bacillus thuringiensis*, a naturally occurring soil bacterium, which potentially mitigates the impact of Bt crops on soil ecosystems.

It is difficult to summarize the results of studies evaluating the impact of GE plants on soil-dwelling organisms because these impacts are tightly associated with the plant, the engineered trait, and the environment (Griffiths, Geoghegan, and Robertson, 2000). The specific soil-associated community is also difficult to characterize. The microbial community found at one field site may be entirely different from that at another field site (Dunfield and Germida, 2001; Blackwood and Buyer, 2004; Muchaonyerwa et al., 2004; Wu et al., 2004; Castaldini et al., 2005; Saxena and Stotzky, 2001; Donegan et al., 1996; Duan et al., 2004; and Milling et al., 2004). The results of studies evaluating soil effects from GE plants thus far suggest that the impact on the microbial and invertebrate communities from GE crops, as compared to conventional

crops, was minor when compared to other factors, such as seasonal and environmental effects (Sanvido, et al., 2006; Milling et al., 2004).

Interactions between the plant and soil organisms may also change due to unintended effects on plant traits and defense abilities, leading to reduced plant fitness. For example, studies have suggested that the application of glyphosate increased populations of various fungi in the soil (Brammall and Higgins, 1987) and also suppressed natural plant defenses and enhanced disease susceptibility in crops and weeds (Wrather, Stienstra, and Koenning, 2001; and Myers et al., 1999). However, further studies have been unable to link glyphosate resistance with disease susceptibility (Sanogo, Yang, and Schrem, 2000). Certainly non-GE plants are not immune to changes in the soil community and disease prevalence due to unpredictable environmental events. Also, it is not clear that genetic modification necessarily makes plants more susceptible to deleterious soil organisms.

Large-scale interactions resulting from standard agricultural practices could influence the incorporation of products from GE plants into the soil and the exposure of soil organisms. For example, the tillage system employed by the grower could influence the amount of interaction that occurs between GE plant-produced proteins and other substances and the microbial community (Angle, 1994). Direct-seed (no-till) cropping systems preserve fertile soil and reduce the amount of sediment that enters streams adjacent to farmland, a major pollutant of streams. A report released by the Conservation Technology Information Center identified the largest growth in no-tillage practice occurring where herbicide-tolerance technology is utilized, achieving weed control through the application of herbicides without damaging the crop (Fawcett and Towery, 2002). No-till systems keep the GE plant material at the surface, limiting contact with soil organisms to those at the surface. On the other hand, with conventional tillage the GE plant material will be incorporated into the soil, potentially diluting the products but also increasing the number of organisms exposed.

(4) Horizontal Gene Transfer

Horizontal gene transfer (HGT) is the natural transfer of genetic material from one organism (the donor) to another organism (the recipient) that is not sexually compatible with the donor (Gay, 2001). Though HGT is thought to be extremely rare, the transfer of chromosomal DNA between bacterial species is considered to represent a significant mechanism for their evolution (Nielsen, Bones, Smalla, van Elsas, 1998). Plant DNA can persist in the soil (Gebhard and Smalla, 1999), triggering concern that transgenes from GE plants may spread horizontally to bacteria.

HGT is relevant to the assessment of risks to the soil environment because of the nature of some of the genes used to develop GE organisms. For example, there is concern that bacterial antibiotic resistance markers, used in the process of selecting GE cells, may undermine the clinical use of antibiotics (Metz and Nap, 1997). Theoretically, resistance could spread to recipient micro-organisms in soil or in the digestive tracts of humans and livestock (Dröge, Pühler, and Selbitschka, 1998). There is general consensus that such HGT from plant tissue to micro-organisms would happen at extremely low frequencies and has not been observed under natural conditions (i.e., in the absence of heavy selection pressure), but must be considered on a case-by-case basis, taking into account the nature of the antibiotic resistance and its occurrence in the environment.

The plant surface and the immediately surrounding environment have been shown to be areas where HGT could occur, likely due to nutrient availability, high humidity, and proximity of colonizing bacteria on the limited growth surface (Björklöf et al,. 1995). Studies have been made of HGT in terrestrial and aquatic habitats by viruses (Kidambi, Ripp, and Miller, 1994) and by natural transformation, the uptake of free DNA into competent bacteria (Bertolla et al,. 1999). Particular elements within the rhizosphere and certain plant exudates can affect transformation frequencies (Nielsen and van Elsas, 2001). However the rate of natural transformation in soil is extremely low; in sterile soil, natural transformation has been shown to occur at rates below 10^{-7} transformants per recipient (Nielsen, van Elsas, and Smalla, 2000) and is estimated to be as low as 10^{-10} or 10^{-11} transformants per recipient in nonsterile soil (Smalla, Borin, Heuer, Gebhard, van Elsas, and Nielsen, 2000). These rates are much less frequent than natural spontaneous mutation rates in bacteria (Drake et al., 1998).

There are a number of mitigating factors that suggest that HGT is not a significant concern when examining the potential effects of GE plants on soil-dwelling organisms. First, several events would have to take place successfully for HGT to occur. In order for natural transformation, that is, uptake of free DNA by soil bacteria, to occur in the soil environment, free DNA needs to be available. The persistence of DNA in the soil was discussed above. There must also be bacteria in close proximity to the free DNA which are capable of taking up the DNA. Some bacteria, called "naturally competent," have evolved the ability to transport free DNA from outside the bacterial cell into the cytoplasm; however, not all bacterial species are competent, and not all competent bacteria are competent all of the time. The transgene must then be incorporated and maintained by the recipient organism (Gebhard and Smalla, 1998). Maintenance of the transgene requires that the alteration is nondetrimental

to the fitness of the organism and therefore, will not be negatively affected by selection.

Transfer of a plant gene to a bacterium does not equal functionality in the bacterium. Regulatory sequences (promoters, enhancers) may not work and introns may not be recognized in the recipient (Conner, Glare, and Nap, 2003). As the risk of HGT from GE plants is considered, it is necessary to bear in mind that the transgene portion of a GE plant's DNA is a very small part of its total DNA. Therefore, the likelihood that a piece of native DNA undergoes HGT is significantly greater than for a given piece of transgene DNA (Conner, Glare, and Nap, 2003).

Second, the antibiotic-resistance genes commonly used for genetic engineering have limited use in treating infections. The most popular selectable marker gene, *nptII*, confers resistance to kanamycin, which has limited therapeutic value as an antibiotic; hygromycin, another antibiotic used in molecular biology, is too toxic for therapeutic use (Conner, Glare, and Nap, 2003). New genetic transformation methods rely less on antibiotic-resistance marker genes, either by using other types of markers or by eliminating marker genes entirely. As a result, the already small potential HGT of antibiotic-resistance genes is likely to continue to diminish in significance.

Third, although HGT between bacteria has been extensively demonstrated in natural systems (Nielsen et al., 1998), no evidence has been found of plant DNA moving to native soil micro-organisms (Badosa, Moreno, and Montesinos, 2004; Heinemann and Traavik, 2004; and Maynard Smith, Dowson, and Spratt, 1991). The lack of information on the abundance of naturally competent bacteria in the environment, frequencies of transformation processes, and environmental factors triggering these processes makes predicting HGT from plants to bacteria difficult (Gebhard and Smalla, 1999). However, the probability of HGT is extremely low, and the evidence, thus far, indicates that HGT does not pose a significant risk for the transfer of traits from GE organisms.

In conclusion, comparing the risks of GE plants and their non-GE counterparts for the management of physical, chemical, and biological aspects of soil ecology is important for sustainability of agroecosystems. The dynamic nature of the soil and its components and the lack of comprehensive research on soil interactions make it difficult to draw any definitive conclusions about the effects of products derived from GE plants entering the system Bruinsma et al., 2002). Traditional agriculture and its associated activities have significant, often detrimental, impacts on soil's abiotic and biotic components, and it is, thus far, unclear whether

introducing GE materials increases or possibly alleviates these detrimental impacts.

c. Genetically Engineered Crops and Potential Impacts on Human Health

In addition to considerations of potential weediness, invasiveness, and soil impacts, another critical focus in assessing the potential risks of GE plants is upon the potential impacts of GE crops on human health. By its nature, this area of consideration is the one which receives the widest public attention.

This section briefly addresses some of the prominent issues associated with the safety of GE crops used as human food and animal feed. The issues addressed in this section, ranging from potential allergenicity and toxicity to nutritional quality, are more thoroughly reviewed in numerous publications and guidance documents that are publicly available. The NRC (NRC, 2004), the Codex Alimentarius Commission (Codex, 2003, 2003), and the United Nation's Food and Agriculture Organization (FAO) and World Health Organization (WHO) (FAO/WHO, 2000, 2001) have developed guidance for assessing the safety of foods derived from GE crops. In addition, numerous other publications are available from researchers and others that address the safety assessment of foods derived from GE crops (Astwood and Fuchs, 1996; Fuchs and Astwood, 1996; Fuchs and Goodman, 1998; Lehrer, Horner, and Reese, 1996; Mendelsohn et al., 2003; Metcalfe, Fuchs et al., 1996; Metcalfe, 2003).

As essential background for this section, it is important first to acknowledge the history of genetic modification and briefly discuss those Federal agencies that have regulatory roles concerning GE organisms and products.

The term "genetic modification" can be used to describe various methods of altering a plant's genetic makeup resulting in the expression of different traits or characteristics than its parent (NRC, 2004). In fact, crop plants have been genetically modified throughout history to produce plants with desired traits (Day, 1996; Kessler et al., 1992; NRC, 2004). Crop developers introduce many new crop varieties intended for food and feed into the market every year that may have characteristics such as insect resistance, higher yield, or improved nutritional attributes (Fuchs and Astwood, 1996; Kessler et al., 1992; Metcalfe, Astwood et al., 1996). Each method of genetic modification, including the two most common methods currently employed—traditional breeding and genetic engineering—requires some level of human intervention (NRC, 2004). Traditional breeding techniques have been employed for centuries, while

genetic engineering became a prominent method of plant genetic modification only late in the 20th century (Kessler et al., 1992; NRC, 2004).

All methods of genetic modification alter a plant's genetic makeup resulting in changes in characteristics such as plant color, flavor, nutrient content, disease resistance, and tolerance to environmental stress (Kessler et al., 1992). While many of the potential changes in the plant's genetic makeup will be intentional, a number of unintentional changes can also occur (Fuchs and Astwood, 1996; Kessler et al., 1992; Metcalfe, Astwood et al., 1996). These unintentional changes can have positive, as well as negative, effects on human health. In most instances, phenotypic changes such as plant color, growth, and production can be identified during the plant breeding and selection process, while some changes such as changed levels of compositional components (e.g., nutrients, allergens, toxicants, and antinutrients) may not be apparent without additional analysis.

Traditionally, new varieties of whole foods have not been subjected to extensive chemical, toxicological, or nutritional evaluation prior to marketing (CODEX, 2003). The regulatory agencies that oversee the safety of food from GE plants do not evaluate food from new, traditionally bred crop varieties for human or animal health safety (NRC, 2004). While most crops naturally produce some level of allergens, toxins, and antinutrients, standard plant-breeding practices allow for monitoring the levels of potentially hazardous substances (NRC, 2004). The history of crop development has shown that, except in very rare instances, these standard crop-development techniques include steps that make it possible to identify potential hazards in crop lines developed for commercialization (Kessler et al., 1992; NRC, 2004; Pastorello et al., 1998).

Unlike traditional breeding, genetic engineering gives developers the ability to move genes into crop plants from organisms that may not have historically been part of the diet of humans and animals. Given this potential, there is some concern about the possibility of moving into a crop used for food or feed a gene whose gene product may be allergenic or toxic (NRC, 2004). While the ability to move potentially toxic or allergenic genes is not unique to genetic engineering, biotechnology techniques can enable the movement of genes between a broader group of species (e.g., plants, insects, and micro-organisms).

The U.S. Government is guided by a Coordinated Framework (51 FR 23302, 1986) which outlines the roles of APHIS, EPA, and FDA in the oversight of GE crop safety. The Coordinated Framework concluded that the products of biotechnology do not differ fundamentally from unmodified organisms or from conventional products; that the product,

rather than the process, should be regulated; that the regulations should be based on the end use of the product; and that review should be conducted on a case-by-case basis. The Coordinated Framework states that no new statutes (laws) are needed to regulate biotechnology products, but that new regulations would be required. While the regulatory authority for APHIS focuses on plant health, both EPA and FDA have responsibility to ensure the safety of human food and animal feed derived from GE plants. EPA is responsible for the human/animal health and environmental safety of any pesticidal substance produced in these plants. FDA is responsible for the safety of the whole food product other than the pesticidal component regulated by EPA.

(1) Potential Allergenicity of Newly-expressed Proteins in Foods Derived from GE Plants

Agricultural crops and the thousands of different proteins that they contain are common components of our food supply. Some of these proteins have been well characterized while others have undergone little or no scrutiny. Nevertheless, we know that humans have been exposed to a wide variety of foods for thousands of years, and consumption of the vast majority of proteins found in foods presents little or no risk of adverse reactions (Metcalfe, Fuchs et al., 1996).

However, there are a number of proteins that have been identified or characterized for their ability to induce allergic reactions (Fuchs and Astwood, 1996). While more than 160 foods and food-related substances have been associated with allergic reactions, a small group of foods including eggs, milk, fish, crustaceans, mollusks, peanut, soybean, wheat, and tree nuts are responsible for greater than 90 percent of allergic reactions in adults (Fuchs and Astwood, 1996). Overall, only a small portion of the adult population—less than 2 percent—is considered to have food allergies (Kimber, Lumley, and Metcalfe, 1997). While the severity of food allergy can vary significantly, when an allergy to a food item is confirmed, individuals are usually allergic to only a few specific proteins in one or two specific foods (Metcalfe, Fuchs et al., 1996). On a percent basis, children have food allergies slightly more frequently than adults, with children being most frequently allergic to milk and eggs. Most food allergies in children disappear by adulthood (Kimber, Lumley, and Metcalfe, 1997; Metcalfe, Fuchs et al., 1996).

Although scientific methods continue to evolve, there is no one test that can be used to assess the allergenic potential of a protein (Goodman et al. 2005; Spök et al. 2005). Because of this, the potential allergenicity of a protein is typically assessed based on its source and structural

characteristics when compared to the structural characteristics of known allergens.

(a) Approaches to Allergenicity Assessment

Several scientific literature reviews focus on engineered foods and food allergy published by members of industry and academia (Astwood and Fuchs, 1996; Astwood, Leach, and Fuchs, 1996; Gendel, 1998; 1998a; Lehrer, Horner, and Reese, 1996; Sampson and Metcalfe, 1992). In 1996, the International Food Biotechnology Council (IFBC), in collaboration with the Allergy and Immunology Institute (AII) of the International Life Sciences Institute (ILSI), published a peer-reviewed report that proposed an approach to evaluating allergenicity of proteins in bioengineered foods (Metcalfe, Fuchs et al., 1996). The approach taken by the scientists participating in this effort used a decision tree for the assessment of potential allergenicity.

In 2000, FAO and WHO convened a Joint Expert Consultation on Foods Derived from Biotechnology and published a report on the safety aspects of bioengineered plants that included a discussion of allergenicity (FAO/WHO, 2000). That report supported the approach to allergenicity assessment described in the 1996 ILSI/IFBC report and adopted a slightly modified version of the 1996 ILSI/IFBC decision tree.

In January 2001, the Joint FAO/WHO Consultation on Foods Derived from Biotechnology was convened specifically to provide scientific advice in relation to the assessment of allergenicity of GE foods (FAO/WHO, 2001). The consultation focused on several items, including the general issues of allergenicity of bioengineered foods, the reevaluation of the decision tree for the assessment of allergenicity of bioengineered foods developed in the 2000 FAO/WHO report (FAO/WHO, 2000), and the development of standardized procedures for the use of the decision tree. After consideration of the current status of scientific information and extensive discussion, these scientists developed a new decision tree. It built upon previous approaches to examining allergenicity but also included several additional strategies. These strategies are targeted serum screening of proteins from sources with no known history of allergenicity, targeted serum screening of protein from sources with no sequence homology to known allergens, the use of animal models, and the elimination of human testing.

In 2003, the Codex Alimentarius Commission adopted internationally accepted principles and guidelines for the evaluation of the safety of foods derived from GE plants, including “Principles for the Risk Analysis of Foods Derived from Modern Biotechnology” and “Guidelines for the

Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants" (Codex Plant Guideline). The Codex Plant Guideline contains an annex on the Assessment of Possible Allergenicity (Codex Allergenicity Annex) (Codex, 2003), which is reproduced below. The Codex Allergenicity Annex acknowledged that there is no definitive test that can be relied upon to predict allergic response in humans to a protein new to the food supply and recommended a "weight of evidence" approach. In the development of this approach, scientific information, previously published allergenicity assessment strategies, and countries' experience in assessing the safety of new proteins in foods derived from GE crops were all taken into account.

ANNEX: ASSESSMENT OF POSSIBLE ALLERGENICITY

Section 1—Introduction

1. All newly expressed proteins[18] in recombinant-DNA plants that could be present in the final food should be assessed for their potential to cause allergic reactions. This should include consideration of whether a newly expressed protein is one to which certain individuals may already be sensitive as well as whether a protein new to the food supply is likely to induce allergic reactions in some individuals.

2. At present, there is no definitive test that can be relied upon to predict allergic response in humans to a newly expressed protein: therefore, it is recommended that an integrated, stepwise, case-by-case approach, as described below, be used in the assessment of possible allergenicity of newly expressed proteins. This approach takes into account the evidence derived from several types of information and data since no single criterion is sufficiently predictive.

3. The endpoint of the assessment is a conclusion as to the likelihood of the protein being a food allergen.

Section 2—Assessment Strategy

4. The initial steps in assessing possible allergenicity of any newly expressed proteins are the determination of the source of the introduced protein; any significant similarity between the amino acid sequence of the protein and that of known allergens; and its structural properties including

[18] This assessment strategy is not applicable for assessing whether newly expressed proteins are capable of inducing gluten-sensitive or other enteropathies. The issue of enteropathies is already addressed in Assessment of possible allergenicity (proteins), paragraph 42 of the Guideline for the Conduct of Food Safety Assessment of Foods Derived from Recombinant-DNA Plants. In addition, the strategy is not applicable to the evaluation of foods where gene products are down regulated for hypoallergenic purposes.

but not limited to, its susceptibility to enzymatic degradation, heat stability, and/or acid and enzymatic treatment.

5. As there is no single test that can predict the likely human IgE response to oral exposure, the first step to characterize newly expressed proteins should be the comparison of the amino acid sequence and certain physicochemical characteristics of the newly expressed protein with those of established allergens in a weight of evidence approach. This will require the isolation of any newly expressed proteins from the recombinant-DNA plant, or the synthesis or production of the substance from an alternative source, in which case the material should be shown to be structurally, functionally, and biochemically equivalent to that produced in the recombinant-DNA plant. Particular attention should be given to the choice of the expression host since post-translational modifications allowed by different hosts (i.e., eukaryotic vs. prokaryotic systems) may have an impact on the allergenic potential of the protein.

6. It is important to establish whether the source is known to cause allergic reactions. Genes derived from known allergenic sources should be assumed to encode an allergen unless scientific evidence demonstrates otherwise.

Section 3—Initial Assessment

Section 3.1—Source of the Protein

7. As part of the data supporting the safety of foods derived from recombinant-DNA plants, information should describe any reports of allergenicity associated with the donor organism. Allergenic sources of genes would be defined as those organisms for which reasonable evidence of IgE-mediated oral, respiratory or contact allergy is available. Knowledge of the source of the introduced protein allows the identification of tools and relevant data to be considered in the allergenicity assessment. These include the availability of sera for screening purposes; documented type, severity, and frequency of allergic reactions; structural characteristics and amino acid sequence; physicochemical and immunological properties (when available) of known allergenic proteins from that source.

Section 3.2—Amino Acid Sequence Homology

8. The purpose of a sequence homology comparison is to assess the extent to which a newly expressed protein is similar in structure to a known allergen. This information may suggest whether that protein has an allergenic potential. Sequence homology searches comparing the structure

of all newly expressed proteins with all known allergens should be done. Searches should be conducted using various algorithms such as FASTA or BLASTP to predict overall structural similarities. Strategies such as stepwise contiguous identical amino acid segment searches may also be performed for identifying sequences that may represent linear epitopes. The size of the contiguous amino acid search should be based on a scientifically justified rationale in order to minimize the potential for false negative or false positive results.[19] Validated search and evaluation procedures should be used in order to produce biologically meaningful results.

9. IgE cross-reactivity between the newly expressed protein and a known allergen should be considered a possibility when there is more than 35 percent identity in a segment of 80 or more amino acids (FAO/WHO 2001) or other scientifically-justified criteria. All the information resulting from the sequence homology comparison between the newly expressed protein and known allergens should be reported to allow a case-by-case scientifically based evaluation.

10. Sequence homology searches have certain limitations. In particular, comparisons are limited to the sequences of known allergens in publicly available databases and the scientific literature. There are also limitations in the ability of such comparisons to detect non-contiguous epitopes capable of binding themselves specifically with IgE antibodies.

11. A negative sequence homology result indicates that a newly expressed protein is not a known allergen and is unlikely to be cross-reactive to known allergens. A result indicating absence of significant sequence homology should be considered along with the other data outlined under this strategy in assessing the allergenic potential of newly expressed proteins. Further studies should be conducted as appropriate (see also sections 4 and 5). A positive sequence homology result indicates that the newly expressed protein is likely to be allergenic. If the product is to be considered further, it should be assessed using serum from individuals sensitized to the identified allergenic source.

Section 3.3—Pepsin Resistance

12. Resistance to pepsin digestion has been observed in several food allergens; thus a correlation exists between resistance to digestion by

[19] It is recognized that the 2001 FAO/WHO consultation suggested moving from 8 to 6 identical amino acid segments in searches. The smaller the peptide sequence used in the stepwise comparison, the greater the likelihood of identifying false positives; inversely, the larger the peptide sequence used, the greater the likelihood of false negatives, thereby, reducing the utility of the comparison.

pepsin and allergenic potential.[20] Therefore, the resistance of a protein to degradation in the presence of pepsin under appropriate conditions indicates that further analysis should be conducted to determine the likelihood of the newly expressed protein being allergenic. The establishment of a consistent and well-validated pepsin degradation protocol may enhance the utility of this method. However, it should be taken into account that a lack of resistance to pepsin does not exclude that the newly expressed protein can be a relevant allergen.

13. Although the pepsin resistance protocol is strongly recommended, it is recognized that other enzyme susceptibility protocols exist. Alternative protocols may be used where adequate justification is provided.[21]

Section 4—Specific Serum Screening

14. For those proteins that originate from a source known to be allergenic, or have sequence homology with a known allergen, testing in immunological assays should be performed where sera are available. Sera from individuals with a clinically validated allergy to the source of the protein can be used to test the specific binding to IgE class antibodies of the protein in *in vitro* assays. A critical issue for testing will be the availability of human sera from sufficient numbers of individuals.[21] In addition, the quality of the sera and the assay procedure need to be standardized to produce a valid test result. For proteins from sources not known to be allergenic, and which do not exhibit sequence homology to a known allergen, targeted serum screening may be considered where such tests are available as described in paragraph 17.

15. In the case of a newly expressed protein derived from a known allergenic source, a negative result in *in vitro* immunoassays may not be considered sufficient, but should prompt additional testing, such as the

[20] The method outlined in the U.S. Pharmacopoeia (1995) was used in the establishment of the correlation (Astwood et al., 1996).

[21] Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (2001): section "6.4 Pepsin Resistance."

possible use of skin test and *ex vivo* protocols.[22] [23] A positive result in such tests would indicate a potential allergen.

Section 5—Other Considerations

16. The absolute exposure to the newly expressed protein and the effects of relevant food processing will contribute toward an overall conclusion about the potential for human health risk. In this regard, the nature of the food product intended for consumption should be taken into consideration in determining the types of processing which would be applied and its effects on the presence of the protein in the final food product.

17. As scientific knowledge and technology evolves, other methods and tools may be considered in assessing the allergenicity potential of newly expressed proteins as part of the assessment strategy. These methods should be scientifically sound and may include targeted serum screening (i.e. the assessment of binding to IgE in sera of individuals with clinically validated allergic responses to broadly related categories of foods); the development of international serum banks; use of animal models; and examination of newly expressed proteins for T-cell epitopes and structural motifs associated with allergens.

(2) Potential Toxicity of Proteins Newly Expressed in Foods Derived From GE Plants

As previously discussed, crop plants contain thousands of proteins and other substances that have become a normal part of the human and animal diet. Fortunately, the vast majority of substances found in crop plants do not cause adverse health effects in humans and animals (Fuchs and Astwood, 1996; Kessler et al., 1992; Metcalfe, Astwood et al., 1996). However, all foods, regardless of their source or method of development, can potentially contain toxins and other dangerous substances. Because of familiarity gained during development of crop plants over many centuries and the inclusion of these crops in mammalian diets, much is known about the toxins, antinutrients, and other undesirable substances that can occur naturally in crop plants (CODEX, 2003; NRC, 2004). In addition to information available in the primary published literature, the Organisation for Economic Co-operation and Development has published a number of

[22] According to the Joint Report of the FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology (22-25 January 2001, Rome, Italy) a minimum of 8 relevant sera is required to achieve a 99 percent certainty that the new protein is not an allergen in the case of a major allergen. Similarly, a minimum of 24 relevant sera is required to achieve the same level of certainty in the case of a minor allergen. It is recognized that these quantities of sera may not be available for testing purposes.

[23] *Ex vivo* procedure is described as the testing for allergenicity using cells or tissue culture from allergic human subjects (Report of Joint FAO/WHO Expert Consultation on Allergenicity of Foods derived from Biotechnology).

consensus documents for a variety of crop plants that provide details about crop biology and composition, including the presence of potentially harmful substances (OECD, 2004).

While it is important to know what harmful substances can be found in our food crops, it is also important to have knowledge about what levels of these substances have been safely consumed in the past and do not pose a threat to human or animal health. This knowledge gives plant breeders the ability to identify breeding lines containing elevated levels of these toxins relatively early in the breeding process and therefore avoid introducing these potentially harmful crops into the food supply (NRC, 2004). This same knowledge is also valuable to crop developers who use genetic engineering as a method of plant genetic modification. An important consideration for GE crop developers is not only what toxins may naturally occur in a plant but also whether there are any unintended changes in the plant as a result of the transformation process that potentially introduces new harmful substances or increases levels of those that naturally occur in the plant (CODEX, 2003; NRC, 2004).
Once an assessment is completed on the plant itself to identify potential unintended changes resulting from the transformation, the safety assessment should then consider the donor, chemical nature, and function of the newly expressed substance (CODEX, 2003; NRC, 2004).

If the GE plant expresses a new protein or other substance that will be present in the food, then the toxicity of that protein or substance may be assessed in several ways. These include conducting an amino acid sequence-similarity comparison to known toxins and antinutrients; studying the substance's stability to heat, processing, and digestion; completing acute oral toxicity tests using surrogate animals (where appropriate); reviewing previous exposures in human or animal diets; and reviewing the identity, source, and function of the substance (CODEX, 2003; EPA, 2000; NRC, 2004, FAO/WHO 2000 [2000 Joint Expert Consultation on Foods Derived from Biotechnology]).

(a) Exposure

As mentioned, it is important to consider whether a substance found in a plant is likely to be harmful; the identity, source, and function of a substance can be useful in determining whether its presence in food is likely to be harmful. If the substance is likely to be harmful, it is important to consider the level of exposure to the substance that is harmful (Day, 1996; NRC, 2004). Assessing whether the level of exposure would be safe can either be accomplished by considering available data based on prior exposure to the substance in the diets of humans or animals or by using surrogate animal testing, which will be discussed later in this section

(CODEX, 2003; NRC, 2004). If the substance has previously been a part of the human or animal diet, then information should be available about history of safe consumption, the levels of exposure that are considered safe, or if there have been adverse effects resulting from consumption of the substance. If there has been no previous exposure, then consideration should be given to how much and in what form exposure to the expressed substance will occur. For instance, consideration should be given to whether the food is processed prior to consumption and, if so, whether processing removes the substance from the food.

(b) Amino Acid Sequence Similarity

Most proteins and other substances that are known to be mammalian toxins have been well studied (Ecobichon, 1993; EPA, 2000; Majak, 1995). The amino acid sequences of many known mammalian toxins have been elucidated and entered into publicly available databases. These databases are powerful tools that can be used as part of the safety assessment for substances expressed in GE plants. An amino acid sequence comparison can be used to identify structural and functional relatedness of a substance to known toxins and antinutrients (CODEX, 2003; EPA, 2000). Therefore, the amino acid sequence comparison can provide valuable information about the relatedness of a substance to a known toxin, and is considered to be an integral part of the assessment of potential toxicity (CODEX, 2003; NRC, 2004).

(c) Digestibility

For proteins found in the mammalian diet, the assumption is that these proteins are broken down into amino acids or peptides as part of the digestion process (EPA, 2000). Stability of a protein to digestion can be assessed using *in vitro* methods in which the protein is subjected to simulated gastric fluid, and then examined by gel electrophoresis (EPA, 2000; NRC, 2004). While *in vitro* digestion alone is not a sole determinant of the potential for a protein to be a toxin, it can contribute to the overall characterization of a protein (CODEX, 2003; EPA, 2000; NRC, 2004).

(d) Surrogate Animal Testing

Unlike the allergenicity assessment for proteins, surrogate animal testing can be performed, when warranted, to assess the potential toxicity of a protein or other expressed substance. The use of animal models, where warranted, can be a significant part of the assessment of the toxicity of substances, such as pesticidal substances, expressed in GE plants (EPA, 2000; NRC, 2004). The use of surrogate animals allows for determination

of whether a substance is potentially a mammalian toxin and at what exposure levels a potential toxin can induce adverse effects. However, there are limitations to the use of animal models, such as when they are used to assess the safety of whole foods (CODEX, 2003). Feeding surrogate animals certain whole foods or diets comprised entirely of one food can induce adverse effects on the animal that are not related to the test substance itself (CODEX, 2003); therefore, the use of surrogate animals may not be appropriate when attempting to identify any potential unintended effects that may occur as a result of genetic engineering.

(3) Composition of Foods from Genetically Engineered Plants Compared to Their Traditional Counterparts

When performing the food safety assessment of a food derived from a GE plant, a key step in the safety-assessment process is the concept of "substantial equivalence." Substantial equivalence does not constitute a safety assessment; rather, it represents the starting point in the safety assessment of a new food, relative to its conventional counterpart. It aids in the identification of potential safety and nutritional issues, and is considered to be the most appropriate strategy for safety assessment of foods derived from recombinant-DNA plants (Codex, 2003). Analysis of key compositional components, along with other data and information, addresses the issue of whether there have been any unintended changes in the composition of the food resulting from the genetic engineering process (NRC, 2004).

Food from each variety of crop developed via genetic engineering should be analyzed to determine the concentrations of key components (e.g., key nutrients, antinutrients, toxins, and allergens). These results should be compared to what are considered normal levels of these components in parental or nontransformed lines of the same crop (CODEX, 2003; NRC, 2004). The Codex Plant Guideline defines key nutrients and key antinutrients as those found in a particular food that may have a substantial impact on the overall diet (CODEX 2003). If this analysis identifies any differences in composition of statistical significance, then these observed differences should be assessed in the context of the natural range of variation for that parameter to determine if the differences have biological significance (CODEX, 2003; NRC, 2004).

4. Examples of Assessing Potential Impacts of Genetically Engineered Plants on the Human Environment

To further illustrate how potential impacts of GE plants on the human environment are assessed, this subsection discusses several examples of GE modifications for specific plant qualities. Accompanying these examples are described the risk assessment issues associated with each of the modifications as discussed.

Plant stress can come from abiotic sources such as temperature or wind extremes, drought or flooding, inadequate nutrition, soil salinity and chemical toxicity, and biotic sources such as weeds, herbivores, pests and diseases. Optimal growth results from an interplay of many factors throughout the growing season or life of the plant, and less than ideal growth effects range from minor to severe, which can result in a lower yield or even total crop failure. A plant weakened by one or more stresses is consequently more susceptible to other stresses. For example, if the soil has an inadequate amount of an essential nutrient, the plant may be less able to defend itself against insect pests, which may, in turn, make the plant less able to resist pathogens such as viruses or fungi.

Although the varying spectrum of factors affecting a growing plant is vast, the plant does not have an infinite repertoire of responses. The ways plants respond to many stresses are now known in considerable physiological and molecular detail, and common mechanisms of response to diverse stresses have been found (Wang et al., 2003; Odjakova and Hadjiivanova, 2001; Singh et al., 2002; Gachamo et al., 2003; van Loon et al., 2006; Kang et al., 2005). This detailed understanding of the mechanisms by which a plant copes with stresses provides opportunities for conventional breeding, as well as genetic engineering, to improve the ability of crop plants to deal with these adverse factors. The following sections discuss examples of GE crops, all intending to improve crop responses to different stresses, and briefly outline some of the potential environmental considerations associated with each trait.

a. Genetically Engineered Insect-resistant Crop Plants

In general, all plants have the ability to repel, destroy, or mitigate pests. While the mechanisms of plant pest resistance remain a mystery in most cases, all plants are resistant to most pests. In other words, plant pest susceptibility is generally the exception (CAST, 1998). For centuries, farmers and plant breeders have used insect and disease resistance genes from wild relatives to improve crop plants. This is, however, an ongoing process because often insects overcome the resistance.

Agricultural biotechnology has increased the number of ways in which plants can made resistant to pests. Since the early 1990s, many biotech companies and public institutions (e.g., government and universities) have

invested considerable research and development efforts on GE plants resistant to insect pests. To date, only insect-resistant plants expressing genes from *Bacillus thuringiensis* (Bt) have been deregulated by APHIS and registered for commercial use by EPA. Bt proteins have been used for more than 40 years as microbial insecticides, which are sprayed on crop plants. However, their use in commercial agriculture has been limited because the proteins are short-lived in the environment, and sprays can protect only aboveground portions of the plant. Genetic engineering of plants that contain Bt proteins in all tissues continuously throughout the growing season has overcome many of the limitations of Bt microbial insecticides.

Bt is a naturally occurring, Gram-positive bacterium found in many environments including soil, insects, stored-product dust, and deciduous and coniferous leaves. There are two current types of Bt proteins used as insecticides: "crystal" proteins and "vegetative insecticidal" proteins. Crystal proteins, called Cry toxins or delta-endotoxins, form within the spores of Bt bacteria. When ingested by a susceptible insect, these proteins readily bind to receptors on the midgut, insert into its membrane (Gill, Cowles, and Pietrantonio, 1992; Schnepf et al., 1998), and form pores causing destruction of cells, leading to starvation, gut paralysis, septicemia (blood poisoning), and death of the insect (Schnepf et al., 1998).

Commercialization of Bt crops has resulted in fewer insecticide applications and thus, lower management costs (Fitt, 2000; Schnepf et al., 1998; Sankula et al., 2005). Also, one notable advantage of GE insecticidal crops over conventional insecticides is the high specificity of the Bt toxins, which minimizes potential toxic effects on nontarget insects (Betz, Hammond, and Fuchs, 2000; Macintosh et al., 1990). Bt crops may also reduce the need for synthetic insecticides which, in turn, would decrease risks to the environment and effects on nontarget organisms, including beneficial insects.

Issues that are typically considered in risk assessment of Bt crops include potential effects on non target organisms, potential unintended effects on the target organism, and potential changes in toxicity and allergenicity (Shelton et al., 2002).

(1) Potential Effects on Nontarget Organisms

As the inserted genes code for insecticidal toxins, there is reason to consider in the risk assessment the question of potential effects on nontarget organisms, including beneficial organisms (Pilson and Prendeville, 2004). The scenarios that would be considered are (1) direct

effects in the case of other insects or other animals eating the GE plants with the Bt gene, and (2) indirect effects in the case of other animals that consume the target insects due to (a) indirect consumption of the Bt toxin or (b) reduced numbers of prey. In the cases of the GE plants with Bt genes to date, the gene products are well known to specifically target a small group of Lepidoptera or Coleoptera (depending on the specific Bt gene). For example, isopods and earthworms can safely consume Bt corn plant residues (Clark et al., 2006; Vercesi et al., 2006). The likelihood of those insects being directly affected by the Bt toxin depends on the size of crop, that is, in cases of small scale field tests, any impact at the population level of affected insects is very unlikely. In cases of large scale commercial use, the estimation of likelihood should consider the presence of potentially affected insects and their feeding behavior on the plant in question.

When sensitive insects are not present in the area of planting or do not use the crop involved as their main source of food, then a significant impact at the population level of those insects is very unlikely. A variety of studies have been done to address this issue and, although some results show a modest effect (Zangerl et al., 2001), most suggest no significant or adverse affects on non-target insects when controls involve insecticide sprayed fields, which is more reflective of actual agronomic practice (Marvier et al., 2007; Sears et al., 2001; O'Callaghan et al., 2005).

(2) Potential Unintended Effects on the Target Organism

The continuous production of Bt proteins on large acreages may increase the potential for target insects to become resistant to Bt proteins through constant selection pressure on target and nontarget susceptible insects (Tabashnik et al., 2003; Tabashnik et al., 2006). These concerns resulted in the requirement of insect resistance management (IRM) strategies for good stewardship of these crops, and EPA has been the lead Government agency regulating IRM for Bt crops. Written reports on various aspects of IRM are submitted to EPA to aid in the evaluation of the success of resistance management for Bt crops. Although information is often shared between EPA and APHIS, most of the IRM materials and reports are not submitted to or reviewed by APHIS as part of deregulation.

An IRM strategy is developed by incorporating several factors into a single plan to delay resistance of target pests to Bt crops (EPA-SAP, 1995)—

- knowledge of Bt proteins, their targets, and their alternative modes of action,
- knowledge of pest ecology and biology,
- appropriate dosages for Bt proteins,

- appropriate refuge design, and integrated pest management (IPM) of the refuge and Bt crop,
- plans for monitoring, reporting, and mitigating incidents of insect resistance, and
- communication and educational strategies on the use of the product.

Thorough knowledge of pest biology is essential to the effective use of plants expressing Bt proteins and to the management of insect resistance to Bt proteins. For example, feeding behavior of the target pest may influence the optimal location within the plant for Bt protein expression, as well as dosage expression. Larval and adult movement (within and between fields, and in overwintering habitats) may affect the types, sizes, and management of refuges developed for IRM. Reproduction (egg-laying habits, mating preferences, and generations per year) will also influence the development of resistance management plans, particularly when implemented to encourage random mating of insects residing in Bt and non-Bt crops.

Another important component of IRM is determining the effective and appropriate dosage of Bt protein. The February, 1998, FIFRA Scientific Advisory Panel (SAP) Subpanel on *Bacillus thuringiensis* (Bt) Plant-Pesticides and Resistance Management determined that a high-dose strategy, together with a refuge strategy, is necessary to mitigate resistance of stalk-boring Lepidoptera (e.g., moths) in Bt corn (EPA-SAP, 1998). A "high dose" is defined as 25 times the protein dose necessary to kill all susceptible lepidopteran insects (EPA-SAP 1998). For coleopteran (beetle)-active Bt products, the definition of a high dose has not been determined, nor has it been concluded that a high dose is necessary to mitigate resistance for these types of insects.

However, within a population of insects exposed to a high-dose strategy, may be a few insects resistant to that high dose of Bt protein. If a crop producing that protein is used repeatedly in the same location, it is theoretically possible for these few resistant insects to multiply to form a larger Bt-resistant population. To minimize the incidence of such large Bt-resistant populations, IRM strategies include the use of refuges or refugia.

Structured refuges are areas containing non-Bt host plants. Insects feeding on these plants will not be exposed to the Bt protein, and Bt-resistant insect populations should not develop on these plants. Refuges therefore provide sufficient Bt-susceptible adult insects to mate with any Bt-resistant adult insects that may survive on Bt crop plants. These matings result in Bt-susceptible offspring which decreases the number of resistant

insects and dilutes the frequency of resistance genes (Tabashnik et al., 2004).

Refuge size, proximity to the GE crop, and refuge management are believed critical for resistance management. Refuge size and location must be structured to maximize the potential for mating between susceptible insects (from the refuge) and possible resistant survivors (from the Bt field). Currently, refuges are planted with a similar hybrid, in close proximity to, and concurrently with, the Bt crop (Shelton et al., 2002). Refuges are treated as needed to control insect pests with non-Bt insecticides or other appropriate IPM practices, and managed according to standard practices in the Bt field.

As more Bt products are commercialized, it is theoretically possible for insect pests to come into contact with multiple Bt insecticidal proteins during their development. If the insecticidal proteins produced by the Bt plants all have similar modes of action, pests may develop cross-resistance (resistance to all proteins using that mode of action) (Tabashnik et al., 1994). One potential method to circumvent or delay cross-resistance is to plant two or more Bt crops, each of which produces a Bt protein with a mode of action different from the others. The theory behind spatial refuges is that it is very unlikely that a pest population would develop resistance to multiple unrelated proteins. However, for many pests, a single individual will only experience a single plant and therefore, a single Bt protein (mode of action) during its development. Because many pest larvae do not move from plant to plant and would not be exposed to multiple Bt proteins, spatial refuges have not been implemented. Other methods for decreasing the likelihood of insect resistance is by incorporating two Bt genes with different mechanisms into a single plant, termed stacking (Zhao et al., 2005) or by altering the toxicity of the protein (Mehlo et al., 2005). The chance that an individual in the population would possess resistance to both mechanisms and escape mortality in order to propagate resistance in the population is exponentially lower than with a single Bt gene. This strategy is only effective if both genes are deployed simultaneously, before resistance has developed in the population to overcome either mechanism.

(3) Monitoring and Mitigation

Identifying populations of resistant insects through a comprehensive resistance monitoring plan is one method to test the effectiveness of resistance management programs and detect the onset of resistance before widespread crop failure occurs. However, monitoring and detecting pest resistance to a Bt protein is a difficult and imprecise task requiring a high level of sensitivity and accuracy. Appropriate resistance monitoring

requires baseline susceptibility data prior to initiation of a monitoring program. In addition to baseline susceptibility data, information is needed to determine how many individuals need to be sampled and in how many locations. The chances of finding resistant larvae in a Bt crop depend on the level of pest pressure, the frequency of resistant individuals, the location and number of samples that are collected, and the sensitivity of the detection technique.

Because there have been no confirmed instances of pest resistance to Bt crops currently planted, there has been no need to implement mitigation measures, and their success has not been evaluated. Mitigation may involve:

- informing customers and extension agents in the affected areas of suspected or confirmed resistance,
- increasing monitoring in the affected areas,
- implementing alternative means to reduce or control target pest populations in the affected areas,
- implementing a structured refuge in the affected areas, and
- halting Bt seed sales in the affected and bordering counties until an effective local management plan has been implemented.

(4) Grower Stewardship

Growers are an essential element for the implementation and success of an IRM plan as they are responsible for planting refuges according to guidelines, and for monitoring fields for unexpected pest damage. Therefore, an education program that informs growers why IRM is needed and provides guidance on how to implement appropriate strategies is necessary. EPA requires registrants to obtain technology use agreements from growers that outline IRM requirements and acknowledges the growers' responsibility to comply with them. The agreement states that growers received a product use guide provided by the company selling the Bt seed. Technical bulletins, grower guides, sales materials, training sessions, Web sites, toll-free numbers for questions or further information, and educational publications have been recommended as tools to educate growers. Educational materials should be consistent and reflect the most current resistance-management guidelines to help ensure compliance with IRM requirements. It takes time and money to comply with IRM requirements, and there is a concern that if IRM requirements are too

complex or time-consuming, growers may avoid planting Bt crops or not adhere to IRM strategies (Langrock et al., 2003).

(5) Potential Changes in Toxicity and Allergenicity to Mammal, Avian, and Aquatic Organisms

EPA-registered Cry proteins have been considered safe because the intestinal walls of mammals do not have the endotoxin receptor necessary for the toxic effect, and the proteins are degraded quickly in the stomach (Sacchi et al., 1986; Shimada et al., 2005; Shimada et al., 2006). Vegetative insecticidal proteins (VIPs) are secreted proteins derived from the vegetative growth stage of Bt. When ingested, the protein binds to midgut cells, attacks the epithelial layer of the midgut, and eventually causes death (Lee et al., 2003). VIPs have a similar mode of action as Cry proteins, but VIPs associate with different midgut binding sites (Cao-Guo et al., 1997; Lee et al., 2003; Yu et al., 1997). Both Bt Cry proteins and VIPs have been deregulated by APHIS, and Cry proteins have been registered for commercial use by EPA.

As part of the ecological risk assessment, EPA also considers potential risks to mammals, birds, and fish. Although wildlife may be exposed to Bt protein, there is no evidence to date that shows toxicity to wild or domesticated mammals, fish, or avian species, and there are no reports of adverse effects from the commercial poultry industry after several years of using Bt corn in poultry feeds (Shimada, 2006a; Taylor et al., 2005). Potential for accidental aquatic exposure from Bt crops is extremely small, and there is no evidence for sensitivity of aquatic species to Bt proteins (EPA–BPPD, 2001). APHIS, as part of its ecological risk assessment, also considers potential risks of GE plants to migratory birds under the Migratory Bird Act and threatened and endangered species under the Threatened and Endangered Species Act.

b. Genetically Engineered Stress-tolerant Plants

Plants have, to various degrees, tolerances against abiotic stresses, such as drought, salinity, and low nutrient availability. While some specialized wild plants, such as succulents, can have high tolerances against stresses, most crop plants are managed with the goal of minimizing environmental stresses.

There is intense interest in the development of drought- and salinity-tolerant plants. The size of the human population is increasing, creating a need for increased agricultural production. At the same time, most prime farmland is already under cultivation and growers are considering the use of more marginal lands. Decreasing availability of fresh water and

changes in rainfall patterns due to climate change provide some of the impetus to modify plants for drought-tolerance. Soil salinity is increasing in irrigated cropland, with approximately 20 percent of such land experiencing salt stress at some level (Yamaguchi and Blumwald, 2005; Yeo, 1998). The increased probability of salt-stress conditions is promoting the development of salt-tolerant plants. The objectives of much biotechnological research, therefore, is to obtain plants that can be grown under dry conditions and on marginal, saline land, leading to increased productivity and reduced use of water in agriculture, which is of particular importance to developing countries (Vinocur et al., 2005).

Another stress-tolerant phenotype being developed is the ability of plants to withstand low levels of nutrient (fertilizer) availability through increased nutrient assimilation or utilization, which has potential benefits in cost and pollution reduction. Increases in nitrogen utilization efficiency of crop plants have the potential to decrease fertilizer costs to farmers by decreasing the nitrogen applications required for adequate yield production, as well as reducing nitrogen runoff and subsequent water contamination (Oliveira et al., 2002). Tobacco modified to increase ammonium assimilation, and thus increase nitrogen efficiency, resulted in plants with greater biomass and leaf-soluble protein compared with non-GE tobacco plants (Oliveira et al., 2002), indicating that increased nitrogen utilization efficiency is possible. Nutrient utilization for phosphorus is also being examined as a potential modification for crop plants. More than 30 percent of cropland experiences phosphorus deficiency (Vance, Uhde-Stone, and Allan, 2003). GE tobacco plants modified for increased phosphorus utilization exhibited significantly greater growth and higher phosphorus concentrations in phosphorus-deficient conditions than nontransformed plants (Lung et al., 2005) and *Arabidopsis* (Xiao et al., 2006). Thus, genetic modifications that alter the assimilation and utilization efficiency of nutrients can result in increased nutrient content of the plant.

Of the more than 15,000 permits and notifications that APHIS has acknowledged or issued, less than 400 applications include plants that have been genetically engineered for stress-tolerance. As this area of biotechnology research continues to move from the strictly experimental to product-development stage, stress-tolerant phenotypes and the mechanisms underlying the tolerance will become more refined and better understood. Subsequently, because insect herbivores show sensitivity toward changes in plant nutrient content, future field studies involving stress-tolerant plants and other GE phenotypes that change plant nutrient or defensive chemical content may have the ability to establish any positive or negative relationships between these GE plants and their insect herbivores.

As the appearance of GE plants tolerant of abiotic stress is a relatively new development in biotechnology, this section can offer only a sampling of the potential effects and does not exhaustively address risk assessment. Issues that would be considered in risk assessment of stress-tolerant crop plants include potential effects on plant-insect interactions and potential changes in weediness.

(1) Potential Effects on Plant-insect Interactions

When plants experience abiotic stress, a multitude of physiological changes occur. For example, when plants experience drought and salinity stress, protein metabolism and amino acid synthesis are impaired (Hsiao, 1973). Under such conditions, existing proteins may be broken down, resulting in increased levels of available nitrogen and amino acids (Brodbeck and Strong, 1987); (Bohnert, Nelson, and Jensen, 1995; Delauney and Verma, 1993). These stress-induced changes in plant physiology are widely thought to positively influence insect herbivores due to favorable modifications in plant nutrient content. In particular, the plant experiences an increase in amino acids and nitrogen (Bentz and Townsend, 2001; Busch and Phelan, 1999) or increase the concentration of other food resources (Chen and Welter, 2002; Richardson et al., 2002).

GE plants engineered for stress tolerance show an increase in nutrient content, either nitrogen or phosphorus, either through accumulation of nitrogen-based osmoprotectants or through more efficient use of nutrients. Although nitrogen has traditionally been recognized as a limiting nutrient for insect herbivores (Mattson, 1980; McNeill and Southwood, 1978; White, 1993), from the few studies that have investigated the effects of phosphorus limitation on insects, there is evidence showing that it can be an important determinant of survivorship (Ayers et al., 2000; Clancy and King, 1993), fecundity (Popp et al., 1989), body size (Busch and Phelan, 1999; Janssen, 1994), oviposition (Skinner and Cohen, 1994), growth rate (Perkins et al., 2004), and population density (Schade et al., 2003). Thus, genetic modifications that result in plants with increased nitrogen or phosphorus content may potentially affect insect herbivore populations on stress-tolerant plants because of the sensitivity of insect herbivores to nitrogen and phosphorus content. It should be pointed out that, although plant-insect actions are relatively well characterized, these effects are not limited to insects. Other plant pests, pathogens or non-target organisms may require similar consideration.

However, not all stress-induced changes in plant physiology will positively affect insect herbivores. Defensive chemical compounds, collectively called “allelochemicals,” are produced by the plant to affect

insect herbivores in a negative manner, such as decreasing survival (Brodbeck and Strong, 1987; White 1993; Gershenzo,n 1984; Inbar, Doostdar, and Mayer, 2001; Mattson and Haack, 1987, 1987). Different insects feed on plants in different ways. For example, some insects chew plant tissues while others suck plant fluids from vascular tissue. Because allelochemicals are much less concentrated in vascular tissue compared to leaf tissue (Raven, 1983), insect species that feed in vascular tissue (sap-feeding insects such as aphids) may respond more positively to plant stress than chewing insects, such as caterpillars, that feed on leaf tissue with higher levels of defensive chemicals (Larsson, 1989). As plants are engineered to become tolerant of abiotic stress, there is a need to consider the complex interactions between GE stress-tolerant plants and insect herbivores.

(2) Potential Changes in Weediness

The ability to tolerate environmental stress enables plants to survive unfavorable conditions. Therefore, one of the key questions for the risk assessments of stress-tolerance traits will be whether they will also change the potential for crop plants to become weedy or cause them to become more invasive. The weediness or invasiveness of a plant depends on many different characteristics such as persistence, reproductive strategy, and dispersal and other factors such as the receiving environment and its climate. As discussed earlier, it is not very likely that a change in one particular trait would suddenly make a plant become weedier. However, it is theoretically conceivable that a change in abiotic stress resistance may incrementally increase the weediness of a plant that already had a number of weedy characteristics. Whether or not this is the case will depend on the characteristics of the plant itself, the phenotypic changes, and the environment to which it will be introduced (receiving environment).

Because plants frequently inhabit environments where water and nutritional resources are limited, the ability to more efficiently exploit these resources may enable a plant to outcompete its neighbors. This ability could result in the development of plants with invasive or weedy characteristics, and the assessment of the impacts from these characteristics would need to include considerations of the impacts of the movement of stress-tolerance traits to the wild relatives of GE crop plants.

c. Genetically Engineered Virus-resistant Plants

Plant viruses represent a significant threat to global agriculture because of their ability to reduce the quality and more important, the yield of food and fiber crops (Hull, 2004; Pappu, 1999). Hundreds of plant viruses have been described, affecting a wide range of plants and trees. In general,

most plant viruses consist of genetic material—either RNA or DNA—enclosed by a protective coat. This coat, which is made from many individual protein molecules ("coat proteins"), plays an important role in protecting the genetic material, as well as determining how the virus spreads. Most plant viruses are obligate parasites (parasites requiring a living host) which move from plant to plant via insect vectors. Additional means of plant virus transmission include fungal transmission, seed transmission, and mechanical transmission, such as grafting (Hull, 2004; OECD, 1996).

In cases where plants are susceptible to viruses, common control or management strategies have included the use of pesticides for control of insect vectors; cultural practices, which include removal of infected plants and plant material serving as sources of viruses; use of virus-free planting material; or use of resistant varieties (Gooding, 1985; Khetarpal et al., 1998; OECD, 1996; Superak et al., 1993; Swiezynski, 1994). While the use of these control strategies has been effective in parts of the world, the overall effectiveness of these strategies can vary significantly from crop to crop and year to year (Hadidi, Khetarpal, and Koganezawa, 1998; OECD, 1996; Pappu, 1999).

Another control strategy shown to be effective is cross-protection (Gonsalves, 1998; Gooding, 1985; Hull, 2004; Sherwood, 1987). Cross-protection involves the ability of a mild strain of a virus to prevent or delay infection by a second more virulent strain of the virus (Culver, 2002; Gooding, 1985; Hull, 2004; Sherwood, 1987). Cross-protection has been attributed to various mechanisms (Culver, 2002; Goregaoker, Eckhardt, and Culver, 2000; Beachy, 1999; Culver, 2002; Goregaoker, Eckhardt, and Culver, 2000; Sherwood, 1987). Coat-protein-mediated cross-protection, for example, relies upon the coat protein to properly associate with and block disassembly of the virulent virus (Culver, 2002). While cross-protection has proven to be effective with some viruses, because of the labor and time needed to infect plants with the mild virus strain, cross-protection is generally not a practical means of controlling virus disease in large-scale or agricultural systems.

In recent years, much of the research and development for controlling plant viruses has focused on development of GE virus-resistant plants. Using the concept of pathogen-derived resistance (Sanford and Johnston, 1985) and cross-protection, genetic modifications of host plants and trees are made that allow for expression of viral genes or proteins in the plant and tree tissue. Plant expression of viral genes or proteins often acts to delay or prevent infection by the same or related viruses. This form of pathogen-derived resistance was first accomplished in 1986 by Roger Beachy and colleagues (Abel et al., 1986). Beachy's team found that

tobacco plants engineered to express tobacco mosaic virus (TMV) coat protein were resistant to TMV infection.

Numerous other virus-resistant plants have been developed and field tested. Most of the virus resistance is based on so-called pathogen-derived resistance, most often using viral coat protein (VCP) or VCP gene expression as the basis for resistance (ISB, 2004; Tepfer, 2002). Over the past 2 decades, nearly 900 field tests for virus-resistant plants (including trees) have been authorized by APHIS in the United States. In addition, several virus-resistant crop plants have been deregulated by APHIS and have been grown commercially. GE virus-resistant plants deregulated by APHIS, to date, include those that express VCP genes (e.g., papaya-ringspot-virus-resistant papaya) or the replicase protein gene (e.g., potato-leafroll-virus-resistant potato) (EPA, 1998; Gonsalves, 1998; ISB, 2004).

While the development and deployment of GE plants has proven to be effective in controlling targeted virus diseases, some concern has been raised about the potential risks associated with agricultural use of GE virus-resistant plants (NRC, 2000, 2002). The safety of these plants has been the subject of numerous scientific meetings and workshops, as well as scientific articles, written by members of the U.S. Government, academia, and industry that address potential risks associated with these plants (AIBS, 1995; Falk and Bruening, 1994; Miller, Koev, and Mohan, 1997; OECD, 1996; Tepfer, 2002).

Potential adverse effects that have been identified and studied in detail include the development of new virus diseases through any of the following mechanisms:

- Heterologous encapsidation (transcapsidation)—the phenomenon where the coat protein of one virus is able to enclose (encapsidate) the nucleic acid of a separate virus. When heterologous encapsidation occurs, there is some potential for altered phenotypes or host range.

- Virus recombination—the exchange of the genetic material between two or more different viruses. If recombination is possible, there is some potential for the generation of new or altered viruses.
- Synergy—the increase in severity of infection or symptoms when two or more viruses infect the same plant. If synergy occurs, the potential result is increased virus disease severity.

- Change in weediness due to gene flow between cultivated crops and weeds. There is some potential for a weedy relative to acquire virus resistance from the crop plant.

While the technology and the analysis of potential adverse effects continue to evolve, currently available scientific data have been used to study these risks (AIBS, 1995; OECD, 1996; Tepfer, 2002). These data and information will be discussed in this section to briefly explore the possible risks and other concerns that have been raised with regard to large-scale deployment of GE virus-resistant plants.

Many of the issues that will be discussed in this section are similar for both RNA and DNA plant viruses. However, to date, the development of GE virus-resistant plants has been mostly limited to plants developed for resistance to RNA viruses (ISB, 2004; Tepfer, 2002). Most GE virus-resistant plants that have been commercialized express the VCPs or VCP genes. Therefore, the focus of this section will be on GE plants expressing VCPs or VCP genes from RNA viruses, although the types of information and considerations will be broadly applicable to other methods of virus resistance. More than 30 different species of plants have been developed for virus resistance and subsequent field testing, with many developed to express genes other than VCP, including replicase protein, nuclear inclusion protein, movement protein, nucleocapsid protein, N gene, helper component, and other virus-specific proteins (ISB, 2004). As plants continue to be developed with genes other than VCP, the agency will assess the safety of these plant–gene combinations on a case-by-case basis, using the same level of scrutiny that has been used for VCPs.

(1) Development of New Virus Diseases Through Heterologous Encapsidation

There are many instances in nature and in agricultural settings where a single host plant is infected by two or more viruses. In fact, some reports about naturally infected plants have identified individual plants that were infected by as many as six different viruses (Abdalla, Desjardins, and Dodds, 1985; Falk et al., 1995). Viruses in a naturally-occurring mixed infection could interact in a number of scenarios. One potential scenario involving VCPs, which can occur in plants co-infected with two or more viruses, is a phenomenon known as heterologous encapsidation (Falk et al., 1995; Miller, Koev, and Mohan, 1997; Waterhouse and Murant, 1983).

Heterologous encapsidation occurs when the coat protein of one virus is able to encapsidate (i.e., surround) the nucleic acid of a second virus. Heterologous encapsidation was first described by Rochow (1970) and has been the subject of numerous reviews (Falk and Duffus, 1981; Falk et al., 1995; Miller, Koev, and Mohan, 1997; Rochow, 1977; Tepfer, 2002). These interactions occur naturally in both agricultural plant and weed plants and are a natural part of virus–virus and virus–plant interactions

(Falk and Duffus, 1981; Falk et al., 1995; Rochow, 1977). In some cases, heterologous encapsidation is a specific interaction between two viruses that plays an important role in both virus biology and survival.

Because the VCP may determine which insect vector is capable of transmitting a particular virus when heterologous encapsidation occurs, the RNA of one virus essentially acquires the phenotypic properties of the second virus for insect transmission (figure 4-1, virions C and D). This observation means that the insect vector recognizes the coat protein, not the RNA inside the coat protein. In other words, the progeny viruses that are the result of heterologous encapsidation often temporarily exhibit new or altered biological properties differing from those of the parental viruses (Falk et al., 1995). The impact on vector specificity is likely limited because many of the heterologous encapsidation interactions that have been identified occur between viruses that are closely related enough that they are transmitted by the same vectors (Hull, 2004).

Once heterologous encapsidation occurs, the potential exists for new or different "exposure" or host range for the RNA of the encapsidated RNA via insect transmission. If this occurs, the result may be one of the following:

- Scenario 1—the virus does not subsequently move.

- Scenario 2—the insect carries the heterologously encapsidated virus to a non-host plant.

- Scenario 3—the insect carries the heterologously encapsidated virus to a host plant, which would be no different than the normal transmission mechanism of the virus.

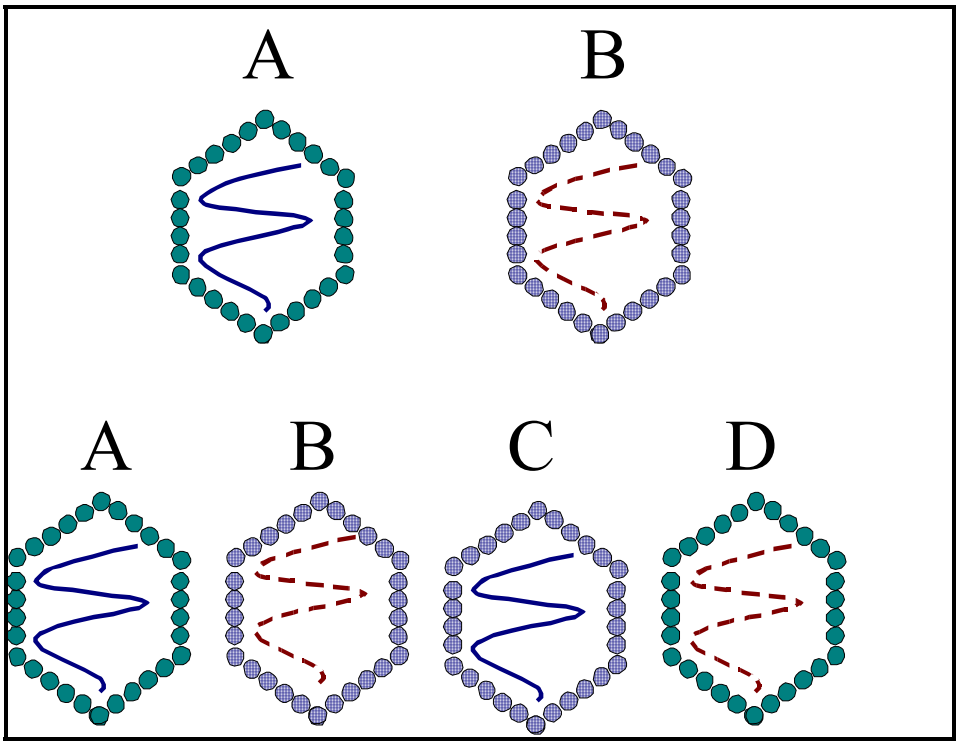

Figure 4–1. Heterologous Encapsidation. Possible outcomes of heterologous encapsidation interactions as previously described by Rochow, 1977 and Falk, 1995. A and B represent the parental viruses. When two viruses co-infect the same cell, the progeny can include virions that are identical to the parental viruses (A and B) or progeny that are composed of the capsid protein of one virus and the RNA of the second virus (C and D).

If scenario one occurs, the virus whose RNA is encapsidated could replicate and move within the plant to which it was transmitted and would subsequently be encapsidated in its own coat protein. However, the virus would not be able to move from that plant via insect transmission because the plant would not likely be a typical host for an insect vector of this virus. In general, the significance of this scenario is transient because once the encapsidated RNA is injected into the host plant, the biological properties of the virus will take over and determine its subsequent fate (Falk et al., 1995; OECD 1996).

If scenario two occurs where the new plant is not a host for the virus whose RNA is encapsidated, it represents a dead-end for the virus. This is because the virus will likely not be able to replicate or move in the new plant. Without the ability to establish an infection—due to its inability to move or replicate—the virus would not likely be transmitted from that plant. Heterologous encapsidation that occurs according to this scenario would not likely be of any ecological significance (Falk et al., 1995; OECD, 1996).

If scenario three occurs, the result would be similar to a typical infection of the encapsidated virus if the virus is transmitted to a normal host of the virus. Once the virus is inoculated into the plant, its normal replication mechanisms would take over and the virus would then produce its own coat protein. However, because the viral RNA was initially transmitted by a different insect vector, it is possible that the virus could be introduced into a host to which it has not been previously exposed. Whether or not the virus would be subsequently transmitted from this host plant would depend upon whether an insect vector was available to transmit the virus. In terms of virus biology, this scenario would not be significantly different from what naturally occurs, other than the fact that the primary inoculation occurred with virus RNA that was the product of heterologous encapsidation. Subsequent virus biology would reflect that of the naturally occurring virus.

Overall, despite the potential for heterologous encapsidation to readily occur in nature, there have only been a few cases in which heterologous encapsidation has been shown to be important in agricultural situations (Falk et al., 1995; OECD, 1996). The likelihood of heteroencapsidation would not be significantly different in VCP-expressing plants (Hull, 2004).

Helper-dependent Transmission

There are a limited number of cases where heterologous encapsidation is a natural part of plant virus epidemiology (Falk et al., 1995). Helper-dependent transmission occurs when one virus exclusively relies upon another virus for heterologous encapsidation for subsequent insect transmission from mixed infections (Falk and Duffus, 1981; Falk et al., 1995; Hull and Adams, 1968; Rochow, 1977). In cases such as carrot motley dwarf, groundnut rosette, and lettuce speckles, the virus diseases are caused by co-infection of the plant by two or more viruses (Falk, Duffus, and Morris, 1979; Falk et al., 1995; Hull and Adams, 1968; Waterhouse and Murant, 1983). In each of these and other virus disease complexes, one of the viruses is insect transmissible and the other is not independently insect-transmissible. The nonindependently transmissible virus relies upon the insect-transmissible virus, via heterologous encapsidation, for insect transmission. In each of the complexes that has been characterized, the insect-transmissible virus is able to replicate and move within the host plant in the absence of the noninsect-transmissible virus. The noninsect-transmissible virus is also able to replicate and move within the host in the absence of the insect transmissible virus; however, the former lacks a coat protein and therefore must rely on the insect-transmissible virus for encapsidation and insect transmission (Falk et al., 1995). While the noninsect-transmissible virus is able to be spread by

mechanical inoculation by itself, it benefits greatly by being associated with the insect-transmissible virus which provides for more efficient dissemination and potentially a wider host range.

Given the crucial role that the coat protein plays in insect transmission and natural plant virus epidemiology, some concern has been raised about whether constitutive expression of viral coat protein in GE plants would increase heterologous encapsidation interactions. Because the amount of coat protein available in GE plants is so dramatically less than the amount of coat protein in virus-infected plants, the potential for heterologous encapsidation is reduced.

Reducing the Risk

Even if one assumes that there is risk associated with heterologous encapsidation interactions occurring in virus-resistant GE plants, the potential exists to reduce ecological impact via modification of the viral coat protein gene (Tepfer, 2002). Research has shown that mutations in the coat protein gene can result in loss of insect transmissibility of the virus (Tepfer, 2002). By incorporating such mutations into the coat protein gene that is expressed in GE plants, the potential for insect transmission of viruses that may have been encapsidated by the plant-expressed coat protein can be eliminated, without affecting the effectiveness of the virus resistance.

(2) Development of New Virus Diseases Through Recombination

Plant virus recombination occurs when the exchange of genetic material between two or more different viruses results in production of a new virus (OECD, 1996; Tepfer, 2002; Worobey and Holmes, 1999). Recombination between viruses in different taxonomic groups has played a significant role in virus evolution (AIBS, 1995; OECD, 1996; Roossinck, 1997; Worobey and Holmes, 1999). In terms of virus evolution, recombination would be considered a frequent event (Hull, 2004). Nucleotide sequence comparisons of different or unrelated viruses have identified similar segments of nucleotide sequence, suggesting that recombination has occurred (Hull, 2004).

Because of the potential for recombination to occur in GE plants, consideration should be given to whether recombinants arising from GE plants would be different from those that arise from mixed infections in non-GE plants, and whether the recombinants are viable (Hull, 2004). Factors affecting the rate of recombination include sequence similarity between the two viruses, the location of the virus within the plant, and structural similarity between the nucleic acids (OECD, 1996). The ability

of a virus arising via recombination to persist in nature depends upon factors such as its ability to replicate or spread systemically or its ability to be transmitted to other host plants (Hull, 2004; OECD, 1996). A significant difference between the potential for recombination in non-GE plants with mixed infections versus the potential for recombination in GE plants is that the virus gene is constitutively expressed, that is, continuously produced in every cell in the GE plant which allows for greater opportunity for interaction and hence, recombination between the expressed gene and the infecting virus (Hull, 2004).

Plant-Expressed Genes-virus Recombination

Looking beyond virus–virus recombination, other studies have focused on whether viral transgenes present in virus-resistant plants can either complement or recombine with viruses that infect the GE plant. In the mid-1990's, Greene and Allison were able to show that such recombination could occur (Greene and Allison, 1994, 1996). Their experiments were the first to show the potential for recombination between plant-expressed genes and viruses infecting that plant. It is not clear, however, from these and subsequent studies (e.g., Borja et al., 1999) how closely these experiments performed under artificial conditions reflect what occurs in natural or agricultural settings with either GE or non-GE virus-resistant plants. In their review of potential recombination in transgenic plants Rubio et al. (Rubio et al., 1999) suggest that the levels of recombination seen in the experiments performed by Borja et al. are orders of magnitude higher than would be expected in GE plants where virus replication is reduced or prevented.

Plant-virus Recombination

Finally, other researchers have shown that over time, plant viruses in natural settings have incorporated various plant cellular RNAs into their genomes as part of their evolutionary process (Karasev, 2000; Masuta et al., 1992; Mayo and Jolly, 1991). In some cases, it appears that once these cellular RNAs become incorporated via recombination, they are subsequently maintained as part of the viral genome.

Overall, given that mixed infections are common in nature, the opportunity for both related and unrelated viruses to interact in natural virus populations is high. Issues such as selection pressure, adaptation to changing environments, competition, fitness, and so forth, likely play significant roles in the various types of recombination that have been identified. These factors also help determine what role the resulting recombinants play in virus biology and epidemiology. Based upon currently available information, it appears that the potential for

recombination in virus-resistant GE plants (i.e., virus–virus and plant–virus) would be similar to the natural occurrence of recombination in virus-infected, non-GE plants (Falk and Bruening, 1994; OECD, 1996; Rubio et al., 1999).

(3) Synergy

Synergy occurs when two independent viruses infect a plant simultaneously and the resulting disease symptoms are more severe than when either virus infects the plant individually (OECD, 1996; Pruss et al., 1997; Tepfer, 2002). Several naturally occurring synergistic virus interactions have been described (OECD, 1996; Pruss et al., 1997; Rochow and Ross, 1955; Tepfer, 2002). Vance and colleagues have shown that when plants are co-infected with both a potyvirus (e.g. potato virus Y potyvirus) and potato virus X potexvirus (PVX), the disease symptoms are significantly worse than when plants are infected with either of the viruses alone (Vance, 1991; Vance et al., 1995).

Subsequent studies have shown that the potyvirus helper-component-protease (HC–Pro) mediates the increase in PVX pathogenicity (Pruss et al., 1997; Tepfer, 2002; Vance et al., 1995). Pruss et al., also showed that the potyvirus HC–Pro can enhance pathogenicity and virus accumulation of other viruses including cucumber mosaic virus and TMV (Pruss et al., 1997). Researchers continue to explore whether other viral proteins or genes play similar roles in virus synergy.

What, if any, risk synergy poses on the environment as a result of the use of GE virus-resistant plants is not entirely clear. However, current scientific data suggest that any impact would be minimal for several reasons. The first consideration is that any effect of synergy associated with a particular GE crop will be limited to the GE plants themselves (OECD, 1996). Additionally, it is not likely that the potential for synergy occurring in GE plants expressing virus genes would be greater than in natural mixed infections (Hull, 2004). Consideration of this type of effect on the GE plant should be included as a part of product development by the plant developer (OECD, 1996; Tepfer, 2002). Potential synergistic interactions could be identified during development of a plant line by inoculating GE plants with widely prevalent viruses of that host plant.

Given the knowledge of the roles that different virus genes play in synergy, developers can also select only those genes that likely would not contribute to synergism or include mutations in such genes so that their potential impact is limited. Genes such as the potyvirus HC–Pro should be avoided, given what is known about its ability to enhance disease development and virus titer of some co-infecting viruses (AIBS, 1995;

Tepfer, 2002). Other genes (e.g., those that might aid in virus replication, movement, or symptom severity) might also be avoided because of their potential to facilitate virus disease development (AIBS, 1995; Tepfer, 2002).

(5) Change in Weediness Due to Gene Flow Between Cultivated Crops and Weeds

Weeds and other noncultivated plants are a primary source of pest- and pathogen-resistance genes. In general, most pest- and pathogen-resistance genes used in traditional breeding for resistance have been found in the centers of origin and areas of diversification of cultivated plants (Khetarpal et al., 1998). These are the areas in the environment where plants have been exposed to selective pressure of pests and pathogens over thousands of years and therefore have developed resistance as a mechanism of survival (Khetarpal et al., 1998).

The potential for introgression of a virus-resistance transgene into a wild or weedy species is another possible outcome of large-scale agricultural use of GE virus-resistant plants. The primary concern is whether transgene introgression would result in a wild or weedy species becoming invasive should the virus transgene make the wild or weedy species resistant to a virus disease that normally plays a role in control of the species (Fuchs, Chirco, and Gonsalves, 2004(a); Fuchs et al., 2004(b); Tepfer, 2002). To take into account the potential risk, several aspects of virus and plant biology should be considered.

As discussed earlier in this section, plant viruses cause significant problems by limiting the amount and quality of agricultural products. Most virus epidemics are the result of a virus or a vector moving from noncrop plants located adjacent to production areas into cultivated crops. Plant viruses are obligate parasites, and as such, total destruction of their plant hosts would lead to the extinction of that virus. Therefore, it is assumed that there is a certain level of tolerance by some hosts—possibly wild or weedy hosts—that allow for persistence of the virus. In fact, many virus infections do not produce visible symptoms in weeds (Hull, 2004). Because of this, there likely exists a number of wild or weedy plant species that contain resistance genes that allow these plants to survive virus infection and serve as reservoirs for the virus (Raybould et al., 1999).

This is somewhat different than the relationship between crops and plant viruses. Most of the major crop species used in today's agriculture (e.g. soybean, rice, wheat, beans) have been subjected to intensive artificial selection over centuries and have only low survival under most natural

conditions. The vast majority of the crops used in agriculture are much less fit, under natural conditions, than wild or weedy plants. Because of this, the impact of virus infection on crop plants is potentially more severe than on many wild or weedy plants.

It is known that gene flow from cultivated agricultural crops to wild and weedy species has occurred since the domestication of a particular plant when sexually compatible wild or weedy species are present (Fuchs, Chirco, and Gonsalves, 2004(a); Stewart, Halfhill, and Warwick, 2003). It is also known that gene flow occurs between virus-resistant GE crops and non-GE crops (Fuchs, Chirco, and Gonsalves, 2004(a)). What is not as well understood is how much gene flow from GE virus-resistant plants to wild or weedy relatives results in introgression of the gene(s) and what ecological impact this introgression would have. Stewart and others discuss the basic difference between gene flow, mediated via pollen or other mechanisms, and introgression of genes, as well as the frequency of introgression and impacts on the frequency (Fuchs, Chirco, and Gonsalves, 2004(a); NRC, 2000; Stewart, Halfhill, and Warwick, 2003). According to Stewart, there have been a relatively low number of confirmed cases of introgression (Stewart, Halfhill, and Warwick, 2003).

However, while confirmatory data may not be available to determine the exact frequency of introgression, there is no clear evidence to indicate that the rate of introgression of a virus-resistance transgene into a wild or weedy species would be any different than introgression of a naturally occurring virus-resistance gene from a non-GE plant (Fuchs, Chirco, and Gonsalves, 2004(a); Tepfer, 2002). Further, there is no evidence indicating that a weedy plant would become more competitive if it gained virus resistance via gene flow from VCP-expressing plants.

Whether or not introgression is considered to be a significant issue with a particular crop or crops, there are steps that can be taken in some circumstances to reduce any potential risk. These include use of plants for which there are no sexually-compatible relatives present in the geographic region; use of plants that have been identified to exhibit low levels of gene flow/introgression; and further development of transgene containment strategies (Stewart, Halfhill, and Warwick, 2003).

Current knowledge and data suggest that gene flow from a GE virus-resistant plant to a wild or weedy plant is not likely to provide different exposure from that which occurs under natural agricultural and environmental settings.

d. Herbicide-tolerant Crop Plants

Weed science became an organized discipline with the introduction of synthetic herbicides in the 1940s (Duke, 1998) and has resulted in an expanding array of new herbicides with increasing efficacy and utility in crop production. The proportion of pesticides used in the United States that are herbicides continues to grow and is now close to 75 percent of the crop-protection pesticide market. While some persistent herbicides can have serious negative impacts on the environment, and in particular on soil and aquatic ecosystems, some of the newer, nonselective and nonpersistent herbicides are less hazardous to the environment.

Over the past few years, several herbicide-resistant crops (HRCs), both transgenic and nontransgenic, have become available in North America (see table 4–1). Plants genetically engineered to be resistant to post-emergence, nonselective herbicides (e.g., glyphosate and glufosinate) are being widely adopted in North America and other parts of the world. HRCs have accounted for nearly one-third of field tests conducted under APHIS authority.

HRCs may offer several advantages to the farmer. In most cases, the farmer can design simpler weed-management strategies based on fewer herbicides (Young, 2006). HRCs resistant to nonselective herbicides are also useful in no-tillage agriculture, allowing the farmer to spray at or near planting and then as needed during crop development (Young, 2006; Pilson and Prendeville, 2004; Conservation Tillage Study, 2002).

There is concern among weed scientists that overreliance on fewer weed-management strategies will result in the evolution of resistance to the more useful herbicides or population shifts to naturally resistant weed species (Young, 2006; Martinez-Ghersa, 2003). Alternatively, overuse of one management strategy may allow other weed species to become adapted in the ecological vacuum created by effective control of the weed species now present.

The occurrence of weeds with evolved herbicide resistance has been documented (http://www.weedscience.org/in.asp). This problem has not yet reached the severity seen with insecticide resistance, but in isolated cases the impact has been significant, resulting in increased weed control and energy costs and reduced crop yields and crop quality.

Table 4–1. Herbicide Resistant Crops Now Available in North America.

Herbicide	Crop	Year Available
Bromoxynil	cotton	1995
Cyclohexanediones*	maize	1996
Glufosinate	canola	1997
	corn	1997
Glyphosate	soybean	1996
	canola	1996
	cotton	1997
	corn	1999
Imidazolinones*	maize	1993
	canola	1997
Sulfonylureas*	soybean	1994
Triazines*	canola	1984

Some scientists propose that resistance to glyphosate and glufosinate herbicide will probably evolve more slowly than to many other herbicides (Bradshaw et al., 1997; Devine et al., 1993), and there are methods, such as crop rotation, to minimize the development of herbicide-tolerant weeds, whether or not the farmer uses genetically engineered HRCs. Most weed scientists agree that with these herbicides, population shifts to naturally resistant weed species will be a bigger problem than evolution of resistance (Owen, 1997). Nevertheless, glyphosate resistance has already appeared in more than one population of ryegrass in Australia (Powles et al., 1998; Pratley et al., 1996).

Introgression of crop genes and transgenes into weeds is possible with some crops and could occur in the case of herbicide tolerance genes. For example, rice can interbreed with red rice (Langevin et al., 1990), a feral form that is a serious weed problem in some rice-growing areas of the world. A herbicide-resistance transgene in a plant can greatly increase the chance of survival of interspecies crosses by eliminating competition of other herbicide-susceptible weeds (Keeler et al., 1996). However, a herbicide resistance transgene alone confers no fitness advantage in areas

where the herbicide is not sprayed. Thus, if the gene is transferred from the HRC to a related weed species, the biggest concern is for the farmer who must cope with the herbicide-resistant weed. In addition, other users of herbicides such as natural resource managers, municipalities and homeowners may eventually be affected, resulting in costs incurred in switching to other weed control methods and herbicide products. There may be environmental costs as well, if these individuals are forced to use herbicides with higher toxicity or higher persistence in order to control herbicide-tolerant weeds.

e. GE Crop Plants Producing Pharmaceuticals and Vaccines

A new development in biotechnology is the production of pharmaceuticals and vaccines in plants ("Plant-Made Pharmaceuticals"—PMPs). A pharmaceutical plant is a plant that has been genetically engineered to produce a medical or industrial product, including human or veterinary drugs, vaccines, antibodies, blood proteins, or enzymes.

This area of research has expanded over the years because PMPs may have advantages in terms of production scale, production costs, ease of storage, and distribution (Ma et al., 2005; Stoger et al., 2005). In addition, the production of pharmaceuticals and vaccines in plants may avoid one of the major disadvantages of pharmaceuticals produced in animal cells, namely, the risk of pathogens in the animal cells that are traditionally used to produce vaccines.

While these potential advantages are generally recognized, this technology poses new challenges especially for the confinement and segregation of these plants. Confinement and segregation are particularly important where there is a possibility of commingling with crops for the food or feed chain. Such commingling with food crops could result in economic losses due to loss of domestic and foreign markets, costs to test for the presence of transgenes, and possible costs for the destruction of commingled commodities.

Pharmaceutical plants fall into a distinct category, and BRS policy makes clear that these GE plants are handled differently than those being developed for use as food or feed. Developers interested in field testing a pharmaceutical plant must obtain permission from APHIS through a permit. APHIS determines permit conditions to ensure appropriate confinement and segregation on a case-by-case basis.

For field tests of pharmaceutical plants, APHIS imposes more stringent confinement measures than for field tests of conventional GE plants, such as increased isolation distances and fallow zones, and increased

inspections and oversight. During the growing season, measures must be taken to achieve reproductive isolation from any sexually compatible plants to prevent cross-pollination with cultivated or wild plants that are not part of the field test. Environmental effects considered include impacts on threatened and endangered species, toxicity of the GE plant to nontarget organisms, and the likelihood of such organisms to be exposed.

f. Silviculture

The United States forest products industry employs 1.6 million people and ranks among the top 10 manufacturing employers in 46 States. The industry generates products valued in excess of $230 billion each year, including $23 billion worth of exports. One-third of the United States is forested (about 747 million acres), and of this total, 350 million acres represent commercial timberland. More than 270 million acres of Federal land have been set aside for use as wildlife refuges, parks, and wilderness areas.[24]

Approximately 2.6 million acres of trees are planted annually in the United States. Approximately 1.6 billion trees are produced, harvested, and shipped by forest-tree nurseries annually. Forest product nurseries produce 852 million trees, private nurseries produce 366 million trees, State nurseries produce 348 million trees, and Federal nurseries produce 38 million trees.

Most forest tree breeding programs are in only the third or fourth generation of tree improvement. The more advanced tree improvement programs were begun in the late 1940s or early 1950s. The species receiving most of the attention in the United States has been loblolly pine in the Southern United States, but there is considerable research with other species, such as slash pine, hybrid poplar, and cottonwood. In the Western United States the dominant species is Douglas fir.

Historically, most tree breeding programs have been conducted primarily using recurrent selection where the best parents are selected to establish seed orchards. The best trees, called "mother" trees, are planted in a seed orchard and are allowed to cross among each other. The seeds that are produced are of higher genetic value than seeds collected in the wild. Over time, the performance of the progeny is evaluated and trees lacking the desired traits can be removed from the orchard. Most trees resulting from such breeding programs are destined for the lumber and paper-pulping industries, so most of the traits that have been selected are related to growth and form. Trees exhibiting rapid growth and good form with

[24] Source of Statistics: American Forest & Paper Association

increased volume are selected to create the next breeding generation. Wood quality has been examined in some species, most notably wood density for pulp yield. Traits such as disease and insect resistance are also selected. For example in loblolly pine, trees are selected for resistance to southern fusiform rust, while *Populus* (poplar) species, are selected for resistance to fungal diseases such as *Septoria* leaf spot or *Melampsora* leaf rust. Resistance to white pine blister rust in pine species in the Western United States is another important trait selected by breeders. Trees that are not intended for timber but for landscape use or production of tree fruits also are improved through breeding programs in a similar manner; however, the desirable traits being selected are different.

Because most tree breeding programs have been in existence only three or four generations only limited progress has been made in domesticating these species. As a result, the trees in breeding programs are not far removed, genetically, from their wild progenitors, and many can intercross freely with their wild relatives. For example, species of *Pinus* and *Populus* are indigenous to the continental United States and have been selected from the wild for tree breeding programs.

Current forest tree breeding programs are moving toward clonal forestry, in which all of the trees planted are genetically identical. Clonal programs are well advanced in some genera, such as hybrid poplar and cottonwood, and are under development in others, such as loblolly and slash pine. By selecting superior clones, substantial genetic gains in wood volume can be achieved, thus allowing more wood to be grown on less land.

Like other plants, trees are genetically engineered using established biotechnological methods that result in stable transgene incorporation. However, tree breeding methods differ in some ways from those used with annual crops, and these differences may affect the deployment of GE tree products. In the immediate future, it is most likely that any deregulated GE trees will be deployed as clones. Assessing the stability of transgenes in GE trees over multiple generations may be more difficult than for row crops because breeding cycles take several years. Also because generation times are long, it may require several years to produce new tree cultivars. Varieties with stacked traits will initially be produced by multiple genetic transformations.

Tree breeders are currently not using GE trees as either pollen or seed parents, orchards using GE trees for the production of GE seeds could be decades away. Therefore, all of the GE trees that are produced for deployment in the near term will be produced by vegetative propagation. This will most likely be done through tissue and cell culture or rooted-

cutting propagation, and new plantations will be established by transplanting vegetative propagules into the landscape.

Forest trees are long-lived perennials. The lifespan of hardwoods and softwoods is decades or centuries. Thus, the duration of a field test of GE trees can span a number of years. Depending on the trait being measured, it could require several years of testing to gather meaningful data.

Many forest trees are wind pollinated, and tree pollen can travel large distances. Pollen from some tree species can live a long time compared to that of many plant species. Therefore, pollen from GE trees could potentially travel for miles from one plantation to another or from managed plantations to unmanaged areas.

In many forest trees, seed dormancy is common. Seeds of some species can remain dormant for years, and in some species stratification, that is, a cold treatment, is required for germination. Therefore, seeds from GE trees could lay dormant for years following harvest and germinate years after deposition on the forest floor.

Genetically improved trees are usually grown in plantations. These plantations cover hundreds to thousands of acres. Plantations are planted in large blocks or mosaics and are harvested when the trees are mature. In a plantation the rotation can range from 8 to 12 years for a genus like *Eucalyptus* to 80 years for long-lived conifers such as spruce or fir. Therefore, a tree "crop" can last for decades.

So, the use of genetic engineering to control tree flowering through sterility is under consideration. Some stakeholders have expressed the opinion that all GE trees will have to be sterile before they can be deregulated. Questions arise as to whether sterility is necessary or desirable. Questions also arise as to whether sterility over a long period of time is achievable and whether redundant methods will be required to ensure long-term stability of a sterile trait. APHIS anticipates that these questions will be answered on a case-by-case basis.

(1) Tree Traits Under Development

Forest trees have a number of insect pests. Some insects attack young trees, and others attack older trees. Annual plants engineered for insect resistance using Bt toxins are grown with refugia to delay the development of resistant insects. For trees engineered for insect resistance, refugia may be useful when grown in a plantation setting. For some species, these resistance genes will need to be effective in plantations for 20 or more years. This timeline could argue for incorporating multiple mechanisms

for resistance into these trees. The potential impact of species that feed on insects that are no longer present in resistant plantations may also have to be considered.

Forest trees are also subject to a number of devastating disease pests. For example, in 1900, the American chestnut was deemed the "Redwood of the East Coast," standing 100 feet tall and comprising approximately 30 percent of the eastern-seaboard forests. A fungal pathogen, accidentally introduced in the late 1800s, resulted in the death of approximately 3.5 billion chestnut trees, and relegated the species to low growing sprouts, unusable as timber.

Resistance to tree diseases, such as fusiform rust in southern pines, is being researched using genetic markers and genomics. There is also a potential for engineering resistance to disease using existing genes. Projects are underway to engineer resistance to blight in American chestnut and to Dutch elm disease in American elm.

Modification of lignin levels and types through genetic engineering of forest trees is a project that is well on its way. These projects are aimed at improving pulping traits or solid wood properties. Changing lignin composition will result in a change in wood chemistry and secondary compounds. These changes could affect resistance to insects and diseases or the ability of the trees to respond to adverse environments. These alterations could also accelerate or slow the rate at which wood decays. These changes would not likely be an issue in a plantation where almost all the wood is harvested but could be an issue if the gene were to escape into native stands.

Lignin is a chemical compound that is an integral part of the cell walls of plants, providing strength. When trees are used for paper production, lignin must be removed from pulp before manufacturing the paper. This extra step is costly, both economically and environmentally (Pilate et al., 2002); thus, poplar trees have been genetically engineered to reduce lignin content (Baucher et al., 1996; Van Doorsselaere et al., 1995). Lignin also has a secondary function as a plant defensive chemical: it reduces leaf digestibility for insect herbivores and functions as a barrier to some pathogens. By decreasing lignin content in GE trees, a possible outcome could be an increase in insect herbivore pest populations (Van Frankenhuyzen and Beardmore, 2004) as well as an increase in disease incidence (Pinçon et al., 2001). However, a small pilot study investigating herbivore and pest pressures on trees genetically engineered for reduced lignin content found no change in insect abundance, a similar variety of insect species within the GE and non-GE plots, and no difference in phytopathogen occurrence (Pilate et al., 2002).

Wood products derived from GE trees would likely be viewed no differently than other non-viable materials derived from GE plants. For example clothing made from GE cotton is treated no differently from that made from non GE cotton. Manufactured wood products, including waste products such as sawdust or wood chips derived from the manufacturing process are non viable and are currently not regulated.

(2) Forest Certification

Large amounts of forest land are bought and sold between companies and other institutions every year. If APHIS adopts a conditional approval process and requires data to be provided once large acreages of GE trees are planted, there will need to be some mechanism to monitor long-term tracking of GE trees as they move from one owner to another.

Several different organizations currently certify forestry operations, that is, there is no one industry standard and programs often compete with each other. Organizations such as the Forest Stewardship Council (FSC, <http://www.fscus.org>), the Sustainable Forestry Initiative (SFI, <http://www.aboutsfi.org>), the Pan European Forest Certification Council (PEFC, <http://www.perf.org>), and the Canadian Forest Certification System (CFCS) are the more prominent organizations. These competing organizations have differing certification standards. In particular some certification programs allow GE trees while others do not. For example, the FSC does not allow the planting of any GE trees, even for testing purposes, on plantations it has certified. SFI has no such restriction. This could cause problems both within the United States and between the United States and other countries, if certified and noncertified products were to become commingled.

Currently no premium is given for products with certification by FSC, SFI, PEFC, CFCS and other organizations. However, more and more companies are looking at purchasing forest products with a "seal" of certification that justify a higher price for a resource or product. Increasingly, retailers of wood and wood products are indicating that they will stock products only if it carries a seal of approval. Consequently mills that have been certified may become the preferred supplier for these outlets. More and more retailers, producers, and forest-based companies are taking the position that they will deal only in goods from certified forest operations.

The sizes of field tests of GE forest trees are smaller, and fewer tests are performed compared to other plants. The current acreages of field tests are relatively small but the duration of the field tests cover multiple years. APHIS has allowed a limited number of GE trees in field tests to flower.

The number of trees that are field tested and the size of field tests is limited by the researcher's ability to monitor for flowering and follow multiple confinement practices. Another limiting factor is that few companies or institutions are at the point of producing large numbers of GE trees for testing.

APHIS has not deregulated any forest tree products, but the agency anticipates that it will be petitioned for the deregulation of a forest tree engineered in the United States within 3 to 7 years. However, entities outside the United States could petition APHIS for deregulation sooner. Worldwide more than 210 field tests with GE trees have taken place, mainly on species such as *Eucalyptus*, *Populus*, and *Pinus*. With the exception of China, none have been deregulated. China has reported the commercial release of GE poplar, with approximately 1.4 million insect-resistant trees planted on 300 to 500 ha[25] (FAO, 2004).

(3) Summary

Unlike crop plants, most of the forest tree species that are being considered for deregulation and deployment in the United States are not far removed from their wild progenitors, and they persist in the environment for a long time. Many can intercross freely with their wild relatives; thus, gene flow can occur from plantations into surrounding forests.

Only a limited number of studies have examined how far pollen can move within and from a tree plantation. Few studies have looked at potential gene flow from GE trees in a plantation to trees in native forests; however some studies have looked at the movement of non-GE markers from an established field test. Because of these limitations the best available data APHIS will have for evaluating the potential for transgenes to move into native forests may be gene flow models from other perennial species, like grasses. APHIS will need to evaluate the applicability of these data on a case-by-case basis, when considering deregulation or conditional approval of GE trees.

For some of the traits that are being engineered into trees, it may not be possible to gather data on the effect of the trait on the environment over many years. A good example would be genes for lignin modification. It will take years to produce such data. Therefore, for some traits, APHIS may need to make certain assumptions or use incomplete data when petitioned for deregulation. When future decisions regarding transgenic trees involve incomplete or unavailable information, APHIS would

[25] Food and Agriculture Organization: Preliminary review of biotechnology in forestry, including genetic modification, (Forest Genetic Resources Working Papers, FRG/59E), Rome: FAO: 2004.

comply with the requirements of CEQ regulations regarding such information (40 CFR § 1502.22).

B. Impacts of APHIS' Current System

This section discusses APHIS' current regulatory system, which is considered the No Action alternative. It first explains how this system serves to protect the environment from potential negative impacts of GE organisms and briefly discusses positive impacts. The system has enabled the authorization of more than 11,000 field tests of GE organisms. A combination of rigorous regulation and aggressive compliance enforcement has resulted in the completion of these field tests with no reported significant impacts to the human environment.

1. Overview of Protections in the Current Regulatory Framework: Confinement of Regulated Articles Until Risk Issues Are Addressed

Most of the GE organisms that are released into the environment for field testing under APHIS authorization and oversight are experimental organisms. Although the agency has years of experience with many of these organisms and the GE traits they contain, there may be some uncertainties in the field testing of these organisms as a result of new and emerging technologies. Acknowledging this, APHIS' response is to protect against significant environmental impacts through a regulatory framework that requires APHIS authorization and oversight of all regulated articles, unless APHIS determines that they pose no plant pest risks. At that time they may be deregulated by the agency. Release authorizations, in the form of notifications and permits, are designed to confine regulated articles such that they do not move outside of the field test site and do not persist beyond the termination of the field test. Thus, confinement forms the cornerstone of APHIS' regulatory approach to these organisms, effectively protecting against the environmental impacts described in section A of this chapter.

Appropriate confinement measures are imposed for each field test, according to the plant and the trait. For example, APHIS guidance for field tests performed under notification recommends isolation distances adapted from AOSCA standards. These standards vary by plant species and are based on the propensity of given plants to cross-pollinate with other plants in the vicinity. Self-pollinating species tend to need smaller isolation distances than species which are pollinated by insects or the wind. Isolation distances can also vary by trait. For example, greater required isolation distances are imposed on field tests of plants engineered to produce substances intended for pharmaceutical and industrial use. In these cases, the increased distance is due to the greater potential impact that any gene flow could have.

It is theoretically possible that field tests of GE organisms could have an impact on the human environment, even if APHIS-imposed confinement measures are effective, due to environmental exposure at the field test site. Such impacts would typically be minimal for a variety of reasons, including the small size of most field releases. However, for field tests that APHIS determines are not categorically exempt under NEPA, APHIS prepares an environmental assessment (EA) prior to authorization to carefully consider the potential impacts of the field test.

After several years of field testing and data collection, a company or researcher may, and usually does, choose to begin preparing for commercialization. At this point, an applicant typically files a petition for the determination of nonregulated status with APHIS, which means they have gathered enough data to demonstrate the new crop variety is not a plant pest and should no longer be regulated by APHIS. Depending on the product, reviews by FDA and EPA may also be applicable. Details of the petition process are described in chapter 1 of this DEIS. Most importantly, as part of the review process, APHIS prepares an EA or an EIS, if necessary, to fully evaluate the organism for deregulation and determine whether it can safely be released in the environment. As with authorizations under notification and permit, the deregulation process is designed in such a way as to evaluate the environmental impacts described in section A of this chapter that may be relevant to that organism.

NEPA requires the preparation of an environmental impact statement for " major Federal actions significantly affecting the quality of the human environment…." The CEQ NEPA implementing regulations provide that "…economic or social effects are not intended by themselves to require preparation of an environmental impact statement. When an environmental impact statement is prepared and economic or social and natural or physical effects are interrelated, then the environmental impact statement will discuss all of these effects on the human environment." 40 CFR § 1508.14. These regulations require the analysis of economic or social effects[26] in those instances when there are significant natural or physical effects on the environment resulting from the action and the potential economic or social effects are closely related to the identified environmental effects.

2. Positive Impacts

This DEIS will not present an in depth analysis of positive impacts, but the agency recognizes that GE organisms can have positive impacts. Therefore, regulating beyond what is necessary to control the risks of

[26] See appendix G for a discussion of the socioeconomic and sociocultural issues that may be associated with genetically engineered organisms.

negative impacts could have the indirect impact of delaying or preventing the use of GE organisms that could have an environmental benefit.

Several examples exist where positive environmental impacts have been attributed to GE organisms that have successfully made their way through the current system of field testing and have been deregulated and commercially deployed. One example is Bt cotton, in which the engineered trait of insect resistance has led to a reduction in the use of toxic chemical pesticides. Another example would be glyphosate-tolerant soybeans. They have facilitated adoption of "no-till" production which saves energy and reduces soil erosion. Other products may provide other economic or cultural benefits (Phipps and Park, 2002). Virus-resistant papaya is often credited with helping to sustain the papaya industry in Hawaii. This is a traditionally important crop to small farms that was being threatened with the papaya ringspot virus.

The agency has strived to keep current regulations in balance with risks, but there are potential areas where regulatory relief may be appropriate. These are discussed by issue in the analysis section C of this chapter where applicable.

C. Impacts of Regulatory Alternatives

This section analyzes the impacts of the various alternatives relative to the current system. The environmental impacts or consequences of implementing the various alternatives are discussed here, along with a comparison and analysis of those impacts. The discussion includes environmental impacts of the alternatives and where appropriate, local and national impacts, environmental effects that cannot be avoided, short-term and long-term impacts, irreversible and irretrievable commitment of resources, and procedures intended to mitigate adverse environmental impacts of program activities.

As mentioned in chapter 1, a decision to revise APHIS regulations may involve many individual changes, and the alternatives will be discussed and analyzed separately in this chapter for the sake of clarity. In this document, the term "alternative" refers to the individual choices that can be made for each issue. These choices collectively comprise the two alternatives: the "Action Alternative" and the "No Action Alternative." The discussion also specifies the significance of direct, indirect, and cumulative impacts. The conclusions presented in this analysis are intended to guide decisionmakers in selecting an alternative for the APHIS program. This chapter will guide decisionmakers in developing the Record of Decision in compliance with NEPA.

Impacts may be evaluated differently depending upon what is being impacted. For example, impacts on humans are considered at the level of one or more individuals. However, impacts on plants or animals are generally considered in terms of the effects on populations, species as a whole, communities, or ecosystems. Impacts on the physical environment are most important when they affect humans or resources important to humans, and certain impacts on resources may have socioeconomic implications. All of these factors were considered in the identification and evaluation of impacts in this DEIS.

Pursuant to the National Environmental Policy Act of 1969 (NEPA), as amended, the Council on Environmental Quality (CEQ) regulations for implementing NEPA, the USDA regulations implementing NEPA, and APHIS' NEPA Implementing Procedures, this evaluation process is used to determine the significance of the impacts. Four factors were considered in the evaluation of biological impacts: the magnitude of an impact, its geographic extent, its duration and frequency, and the likelihood of its taking place. By considering each of these factors, the evaluation of impacts is kept uniform and systematic. Where a quantitative evaluation is possible, specific criteria for the magnitude, geographic extent, duration and frequency, and likelihood of impacts are used. Where quantitative evaluations are impossible, qualitative comparisons of impacts are used.

1. Issue 1

APHIS is considering the broadening of its regulatory scope beyond genetically engineered organisms that may pose a plant pest risk to include genetically engineered plants that may pose a noxious weed risk and genetically engineered organisms that may be used as biological control agents. Do regulatory requirements for these organisms need to be established?

Given the rapid advances in biotechnology, the present scope of regulations may not be of sufficient breadth to cover the full range of GE organisms and the full range of potential agricultural and environmental risks posed by these organisms, including risks to public health. Historically, APHIS has used only the authority in the PPA that was originally granted in the FPPA and the PQA. Specifically, the agency has used its authority to protect against plant pests as the basis for regulating GE organisms. The PPA, however, redefined authorities and responsibilities for the agency. Changes are now being considered in recognition of these responsibilities and in light of these new technologies.

Alternatives Related to Issue 1

1. No Action—continue to regulate GE organisms as potential plant pests and use genetic transformation as the trigger for regulation (event-by-event).

2. Expand the scope of what is regulated by adding considerations of noxious weed risk and regulating GE biological control organisms in addition to evaluating plant pest risks, and use genetic transformation as the trigger for regulation. Continue to regulate event-by-event.

3. Expand the scope of what is regulated by adding considerations of noxious weed risk and regulating GE biological control organisms in addition to evaluating plant pest risks. Use novelty of the trait in the species as the trigger for regulation.

In addition, the following alternative could be used in conjunction with any of the above to exclude certain organisms based on risk:

4. Exclude specific classes of highly familiar organisms and highly domesticated, nonweedy crop plants and also create a mechanism to exclude additional organisms from the definition of regulated article after a safety review.

a. No Action Alternative

Under this alternative, APHIS will continue to regulate GE organisms, on an event-by-event basis, for their potential to pose plant pest risks, and use genetic transformation as the trigger for regulation. Regulating GE organisms as potential plant pests has provided effective protection to the environment and to American agriculture. APHIS knows of no impacts that have occurred as a result of limitations in the agency's authority. However, it is arguable that some GE organisms that may pose a risk to public health, agriculture, or the environment may not meet APHIS' definition of a regulated article. Specifically, APHIS' authority could be challenged in cases where there are no plant-pest sequences and for which there is no "reason to believe" that the organism poses a plant pest risk. The agency has been confronted with proposed introductions of GE organisms, such as algae, which the current regulations appear not to cover. While the organism may very well not pose a significant danger, the agency is not in a good position to make such an argument due to lack of familiarity.

For example, if GE organisms could be released into the environment without regulatory oversight due to a narrow definition of a regulated article, there could be negative impacts on agriculture due to genetic traits that increase plant susceptibility to disease or insect pests. Similarly, if a GE organism were released into the environment due to a gap in APHIS' regulations and if the GE organism were to become persistent in the environment, pesticide usage might increase to effect the eradication of the organism. However, because of the difficulty in predicting innovations in genetic engineering technology, the exact nature and size of these hypothetical environmental impacts are uncertain.

b. Action Alternatives: The Scope of Regulations

Impacts resulting from the field testing of GE organisms would likely increase in number and significance if a growing number of GE organisms with the potential to cause environmental harm were released into the environment because APHIS had no regulatory oversight and therefore, could not impose safeguards. As technology continues to advance and the variety of genetic material moved between species continues to increase, an expansion of regulatory oversight, based on existing statutory authority, could reduce the frequency and magnitude of environmental impacts. In alternative 2, APHIS would continue event-by-event regulation that considers potential plant pest risks and add considerations of noxious weed risks and regulating GE biological control organisms. Under this alternative, APHIS oversight would expand to cover all genetically engineered plants as well as all potential plant pests. APHIS recognizes that this expansion might result in regulation of classes of organisms that could be deemed safe in the future. Therefore, for this alternative, it might be appropriate to consider that certain organisms could be excluded from the definitions and removed from APHIS oversight as described below.

Alternative 3 is a trait-based approach. Under this alternative, APHIS would still rely on one or more provisions in the PPA, regulating GE organisms based on their potential as plant pests or noxious weeds or both. However, it would be assumed that any GE organism with an unfamiliar plant/trait combination might pose a risk covered under the act; therefore, all GE organisms would initially be subject to APHIS oversight. To determine whether oversight is actually necessary, the key questions are whether APHIS is familiar with a particular organism expressing a particular transgene or group of transgenes and whether the organism is sufficiently safe to be removed from APHIS oversight. This approach differs from the current approach in the treatment of deregulated GE organisms. In the trait-based approach, once a GE organism was found to be safe and was deregulated, new transformants representing the same familiar plant/trait combination could also be deregulated. The system

should be as protective as the current one, except that it would not account for unanticipated changes relating to the transformation process or other differences that may exist at the biochemical level among plants having the same phenotype. Based on experience, the probability of unanticipated changes appears low. To address this small risk, an applicant might be required to produce an abbreviated data package to show that there are no unanticipated phenotypes.

Both alternatives 2 and 3 above allow the expansion of APHIS' regulatory scope to reduce the chances that a GE organism, the field testing of which may pose environmental impacts, will fall outside APHIS' purview. Although each of the proposed alternatives sets different criteria for the determination of whether a GE organism would be regulated, the adoption of either of the proposed alternatives would increase the number and types of GE organisms that would be regulated. Increasing oversight of GE organisms that may pose a risk to the environment will be more protective of the environment and should reduce environmental impacts which might otherwise occur should the agency elect the No Action alternative. Although the level of public safety provided by the current regulatory system has been demonstrated over the course of its history, the advances in genetic engineering technology are rapid, inevitable, and to some extent, unpredictable, which could result in the production of GEOs that pose a risk but are outside of the current regulatory scope. Therefore, the No Action alternative potentially poses a greater risk of adverse environmental impacts to many of the environmental factors under analysis than either of the other proposed alternatives.

Alternatives 2 and 3 create regulatory systems that allow APHIS to address new and emerging issues as genetic engineering technologies continue to advance. Both of these alternatives would enable APHIS to reduce the risk of introducing potentially harmful GE organisms and the risk of environmental impacts resulting from the introductions. Therefore, the adoption of either of the proposed alternatives should result in a reduced potential for significant adverse impacts to the environment as compared to the current system.

Between the two alternatives, the event-by-event approach using the new provisions of the PPA may result in APHIS examining a larger number of GE organisms than it would using the trait-based approach. This is because with a trait-based approach, entire classes of GE organisms could be removed from APHIS oversight, whereas, with event-by-event regulation, each GE organism is considered individually. However, selecting either alternative should enable APHIS to exercise regulatory oversight for all genetically engineered plants initially, including algae and other noncrop species, as well as all micro-organisms and invertebrates.

c. Action Alternatives: Methods to Exclude Certain Organisms Based on Risk

APHIS is also considering whether the new regulations should designate specific articles as excluded from regulation. This is alternative 4. The purpose of this provision is to remove from regulatory oversight articles with which APHIS has a great deal of familiarity and which have a long, well-documented history of safe use or articles, such as plants with altered flower color or similar traits, with no potential to cause significant environmental impacts. The exclusion process would be rigorous and NEPA-compliant, and would provide opportunity for public comment. This alternative could be adopted in conjunction with any of the other alternatives.

APHIS would not exclude any organism from regulation unless it determined that exclusion of the article would have no significant adverse impacts to the human environment; therefore, a regulatory provision allowing exclusions should not have any significant adverse environmental effects.

2. Issue 2

APHIS is considering revisions to the regulations to increase transparency and to address advances in technology that may create new products and concerns. Should a new system of risk based categories be designed to deal with new products and new concern? If so, what criteria should be used to establish the risk-based categories?

There is public interest in understanding how APHIS regulates various types of organisms according to risk and familiarity. In addition, there is a trend toward more highly varied organisms, and the risk assessment process may need greater flexibility to handle this variety. The current system of notifications and permits needs to be more transparent to the public, and developers have a vested interest in knowing how organisms that they are developing will be regulated. In addition, the term "notification" has proven somewhat misleading in that it does not clearly convey that these field tests are subject to full APHIS oversight: no GE organisms may be imported, moved interstate, or released into the environment without active approval from APHIS. In recognition of the issues above, the agency is considering risk-based categories in which GE plants are classified according to risk and familiarity so that oversight and confinement vary by category. Redefined categories may provide added flexibility to better regulate diverse organisms and new types of traits and provide better clarity to the regulated community and to the public, which may, in turn, promote greater confidence in the system.

Alternatives Related to Issue 2

1. No Action—continue to use a two-tiered system (notifications and permits).

2. Abolish categories and treat all incoming requests on a case-by-case basis.

3. Establish a tiered permitting system for all organisms based on newly devised criteria.

4. Establish a tiered permitting system for plants based on newly devised criteria and evaluate permit applications for introductions of nonplant organisms on a case-by-case basis.

a. No Action Alternative

For this issue, the No Action alternative is to continue with the two-tiered system for introductions, which consists of permits and notifications. APHIS has been able to meet the demands of the technology and adapt to a wide range of organisms field-tested under the permit system. To date, the two-tiered permitting system has been effective at managing risks associated with introductions and preventing significant environmental impacts.

b. Action Alternatives

Alternatives 2, 3, and 4 have been proposed as revisions to APHIS' current method of authorizing the movement and field testing of GE organisms. Alternative 2 treats each organism/gene combination on a case-by-case basis. Instead of establishing permit types for different categories of GE organisms, there would essentially be only one type of permit. Every GE organism proposed for movement or field testing by an applicant would be evaluated by APHIS, the potential impacts to the human environment would be determined, and APHIS would fashion individual permit conditions for that GE organism. Each permit issued under this scheme would be unique, and each GE organism would be regulated uniquely.

Alternative 3 would establish permit tiers for requests of all incoming organisms based on risk and familiarity and use a case by case approach within all risk tiers but the lowest. APHIS has extensive experience that could be drawn upon to establish such a system for plants, but establishing such a system for other types of organisms might be more difficult at this time. A system which misclassified a GEO might result in risks to the

environment because oversight and confinement of that GEO would be based on the tier type to which it was assigned.

Alternative 4 is similar to 3 above and establishes permit tiers for plants, but handles all other types of organisms on a case-by-case basis.

Table 4–2 is an example of a tiered permit system for GE plants consisting of four tiers. The first tier, Type 1 permit, is proposed for most of the crops that would currently qualify for notifications. APHIS envisions that the eligibility criteria will borrow from APHIS' existing list of plant pest-based notification criteria, and also incorporate new considerations based on the noxious weed provision. Examples of the criteria might be as follows.

Criteria for Plant Permit Type 1:

1. The regulated article is any plant species that is not on the Federal list of noxious weeds in regulations at 7 CFR part 360 under the PPA (7 U.S.C. § 7712), and, when being considered for field testing, the regulated article is not expected to establish and propagate outside of the managed ecosystem. Examples of organisms that might not qualify for this reason are open-pollinated turf and forage grasses, forest trees, and aquatic plants.

2. The genetic material is introduced using a method that has been demonstrated to result in integration of the new sequences into the plant genome, as defined in 7 CFR § 340.1.

3. The function of the introduced genetic material is known and its expression in the regulated article does not result in plant disease.

4. The introduced genetic material does not:
   - Cause the production of an infectious entity, or
   - Encode substances that are known or likely to be toxic to nontarget organisms known or likely to feed or live on the plant species, or
   - Encode substances with whose function APHIS is unfamiliar (e.g. substances intended for pharmaceutical or industrial use).

5. To ensure that the introduced genetic sequences do not pose a significant risk of the creation of any new plant virus, plant virus-derived sequences must be:
   - Noncoding regulatory sequences of known function, or
   - Sense or antisense genetic constructs derived from viral genes from plant viruses that are prevalent and endemic in the area where

the introduction will occur and that infect plants of the same host species and that do not encode a functional noncapsid gene product responsible for cell-to-cell movement of the virus.

6. The plant has not been engineered to contain the following genetic material from animal or human pathogens:
   - Any nucleic acid sequence derived from an animal or human virus, or
   - Coding sequences whose products are known or likely causal agents of disease in animals or humans.

7. If the GE plant is a food crop, any introduced protein either: (1) has a pesticide tolerance[27] from EPA if it is a plant-incorporated protectant, or (2) has been evaluated for key food safety issues of toxicity and allergenicity. This requirement should be fulfilled before total planted area of tests exceeds 10 cumulative acres in a single year.

8. The plant does not have sexually compatible relatives that are threatened or endangered.

9. The proposed test site is not in a habitat designated as critical for a threatened or endangered species.

Crops not qualifying for the Type 1 tier would go into the remaining tiers based on potential risk and familiarity, with the highest tier, Type 4, being used in cases where there is a likelihood that the plants or their transgene products would be highly toxic to vertebrates, they would go into the Type 4 tier. Criteria for the four permit types are listed in column 1 of table 4–2.

Tier definitions would be based on potential risks and familiarity with the organisms. Familiarity is important because unfamiliar organisms may pose risks that the agency does not currently recognize and of which the agency has little mitigation experience. Because the tiers are associated with risk and familiarity, the degree of confinement and oversight vary by tiers. Specific regulated articles will be assigned to tiers so that appropriate permit conditions, confinement measures, and compliance requirements will be imposed to ensure that the impacts resulting from the introduction of the article do not significantly impact the human environment.

[27] See EPA's "Regulations Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants" at http://www.epa.gov/pesticides/biopesticides/pips/pip_rule.pdf .

For example, some pharmaceutical and industrial plants might be found neither toxic, allergenic, otherwise biologically active in humans, nor dangerous to the environment if fully evaluated by all relevant agencies. However, until such findings have been made, APHIS would issue Type 3 permits for these plants in acknowledgement of the unknown potential for serious harm. Thus, the proposed Type 3 assignments for this category reflect APHIS' view that there is less familiarity with these plants than those assigned to Type 2, and the Type 3 tier provides the strict-confinement approach the agency feels is prudent, given the nature of the organisms. Also, many plants that are placed in the Type 2 tier may not be of higher risk than those in Type 1, but simply of low familiarity. Type 2 offers increased flexibility for plants with which APHIS has less familiarity and allows confinement to be tailored as needed, as is currently done for permits. The permit tiers will have different oversight with respect to confinement, reporting, and other requirements.

An important feature of the proposed tiered permitting system is the proposed elimination of the need for a permit for interstate movement of some GE plants. Plants that would qualify for field testing under a Type 1 permit would not require an interstate movement permit. Instead, the agency is considering a process through which individuals would notify the agency that they plan to transport the organisms. No agency response would be required. APHIS would still regulate the types of containers used to safely transport the organisms. No environmental impacts are envisioned from this change because no escape or dissemination of the plants is expected. Information collected from transporters during shipping would serve a tracking function for States and other entities interested in the development of biotechnology products.

In terms of risk management and environmental impacts for the regulated introduction of GE plants, the end result of adopting a permitting system based on case-by-case evaluation or one employing tiers should be the same. In either situation, an APHIS biotechnologist would assist the applicant in the development of procedures and permit conditions that would ensure the confinement of the GE plant and minimize its potential impacts on the human environment. This has always been the goal of APHIS' regulation of GE organisms, and more than 15,000 field tests have been successfully permitted in this way without significant adverse environmental impacts.

Table 4–2. Tiered Permit System for Environmental Releases of GE Plants

Permit Classes of Genetically Engineered Plants	Procedural Requirements for Permits	Permit Conditions
Type 1 • Plants having a low potential as plant pests [and noxious weeds] based on meeting criteria including a food safety evaluation of newly expressed substances, unless acreage is very low.[28] • Plants reclassified from Type 2 based on high familiarity.	• Information requirements: Simplified format(s). • Review by BRS: Applications reviewed for compliance with criteria. • Scope of permits: Required only for field tests, single year.	• Confinement: APHIS presets standard confinement requirements as part of permit conditions. Confinement will be similar to that typically used for field tests for notifications under current system. • Inspections: A percentage is chosen for inspection.
Type 2 • Plants having higher plant pest [or noxious weed] potential than Type 1. • Food crop plants reclassified from Type 3 based on increased familiarity. • Nonfood crop plants engineered to produce traits with which APHIS is unfamiliar (e.g., pharmaceutical and industrial nonfood crops).	• Information requirements: Standard formats. APHIS may ask additional information. • Review by BRS: Case-by-case. • Scope of permits: Single- or multi-year permits with SOPs.[29]	• Confinement: Variable, depending on plant. For most, applicants will propose confinement standards for APHIS review (modified as necessary). Plants reclassified from Type 3 will follow APHIS-set standards consistent with those currently used for pharmaceutical and industrial plants • Inspections: At least one per permit.
Type 3 • Plants having higher plant pest [or noxious weed potential] than Class 2. • Food crops engineered with traits with which APHIS is unfamiliar (e.g., most pharmaceutical and industrial plants) or expressing substances having food safety profiles with which APHIS is unfamiliar.[30]	• Information requirements: Standard formats. APHIS may ask for additional information. • Review by BRS: Case-by-case. • Scope of permits: Single- or multi-year permits with SOPs.[31]	• Confinement: Very stringent standards likely to exceed those currently used for pharmaceutical and industrial plants. • Inspections: Up to 5 annual inspections.
Type 4 • Plants with highest plant pest [or noxious weed] profile, i.e. likely to pose a hazard to human health and environment (e.g., production of a compound known to be highly toxic to humans or other vertebrates or known to cause severe allergenic reactions in some people.)	• Information requirements: Standard formats. APHIS may ask additional information. • Review by BRS: Case-by-case. • Scope of permits: Single-year permits.	• Confinement: Highly stringent, case-by-case. Security/surveillance and restrictive access will be required. • Inspections: Not yet determined. At least as often as Type 3.

[28] See text for complete listing of eligibility criteria.

[29] Appropriate for production and routine multi-year research. APHIS reviews initial permit and SOPs, applicant required to submit changes to APHIS for approval.

[30] Examples of what APHIS will consider in determining familiarity: 1) Agency experience with the gene product, trait, or similar traits. APHIS currently has extensive experience with many agronomic and product quality traits. 2) Key food safety issues of the new substance have been evaluated. 3) Origin of the gene (e.g., food crop vs. other). APHIS envisions that most pharmaceutical and industrial compounds will be placed into class 3 initially, but may be moved to other classes as the agency gains experience.

[31] Appropriate for single- or multi-year research as appropriate. APHIS reviews initial permit and SOPs, applicant required to submit changes to APHIS for approval.

The adoption of any of the proposed alternatives, including the No Action alternative, will not change this level of impact; APHIS would continue to exercise appropriate oversight to ensure that all GE organisms released into the environment are safe. APHIS would continue to perform NEPA-compliant environmental analyses when a proposal to introduce a GE organism raises new issues with which APHIS lacks familiarity.

As APHIS gains more experience with GE organisms other than plants, it may be possible to incorporate these into a tiered system as proposed in alternative 3, but APHIS' current level of experience with these organisms is much less than with plants. Moving from a case-by-case analysis for nonplant GE organisms to the type of tiered system proposed for plants is, therefore, premature and could result in negative environmental impacts. As for the approach to GE plants, the major differences between alternatives 2 and 4 are administrative. APHIS expects a case-by-case approach which includes low risk plants would be more resource intensive than the current system, thereby, increasing regulatory burdens.

For example, the notification system requires a fixed data package from each applicant. If every GE plant currently field-tested under a notification were to instead receive an individual evaluation, APHIS would necessarily need an individual data package with each field test application, although APHIS does not anticipate that such additional data would make this approach more protective of the environment than the current approach or than the multi-tiered approach proposed for GE plants. Also, case-by-case evaluations may seem less predictable to the regulated community and less transparent to the public. This may make it more difficult to predict how long a particular permit application would require for its evaluation, and the resultant permit conditions may be more difficult for the applicant to anticipate.

3. Issue 3

APHIS is considering ways to provide regulatory flexibility for future decisions by accommodating commercialization of certain genetically engineered organisms while continuing, in some cases, to regulate the organisms based on minor unresolved risks. Other regulated articles could be treated as they have been under the current system, in which all regulatory restrictions are removed. What environmental factors should be considered in distinguishing between these kinds of decisions?

Once an article has been deregulated, APHIS cannot place any restrictions or requirements on its use, short of re-regulating the article. Restrictions and requirements have not been deemed necessary in the past because BRS risk assessments have concluded that the GE plants APHIS has deregulated pose no greater risks than conventionally bred plants.

However, APHIS recognizes that future development and commercialization of plants with less familiar traits may pose new challenges for the agency because even a thorough assessment may not resolve all unknowns regarding an article proposed for deregulation. These unknowns may justify continued scrutiny and data collection or use restrictions, even while allowing planting of the article without a permit. Therefore, APHIS is exploring a system that could give increased flexibility for handling special cases involving less familiar traits by creating provisions that allow for imposition of conditions for unconfined release. This could facilitate commercialization, while requiring appropriate restrictions or monitoring.

Alternatives Related to Issue 3

1. No Action—continue with a system granting full nonregulated status to crops that removes them from all regulatory obligations under 7 CFR part 340.

2. Continue to allow for the option of granting full nonregulated status and develop appropriate criteria and procedures through which crops can be removed from permitting but some degree of agency oversight as necessary to mitigate any minor risks is retained.

a. No Action Alternative

The No Action alternative for this issue is to continue with a system of deregulating GE organisms to remove them from all regulatory obligations under 7 CFR part 340. Currently, a GE organism is not deregulated until a thorough APHIS review concludes that it poses no plant pest risks. APHIS has the authority to deregulate in part, but has not used this approach to date.

This approach is highly protective of the environment. Because the agency cannot attach conditions or risk-mitigation measures after full deregulation, this approach requires that the agency determine that the use of the regulated article poses no plant pest risks. If all such risks cannot be resolved, the organism must remain under regulation, requiring permits or notification.

b. Action Alternative

Under alternative 2, APHIS would develop processes and appropriate safety criteria to retain oversight, when appropriate, of a GE organism after it has otherwise been approved for unconfined release through either deregulation *in part* or some new mechanism designed to deliver such

flexibility. Partial deregulation could be granted when APHIS determined that minor questions remained regarding the regulated article that could be managed with appropriate conditions so that environmental impacts would not be significant. An applicant could petition for partial deregulation, or the agency could grant partial deregulation in response to a petition for full deregulation.

The potential for environmental impacts due to the implementation of partial deregulation comes from the possibility that an organism may receive partial deregulation and undergo widespread planting before any negative environmental impacts could be detected. First, this possibility is extremely remote because applicants cannot apply for deregulation until years of laboratory, greenhouse, and field data have been collected. Applicants must establish the agronomic and environmental equivalence of the regulated article to the non-GE version of the organism.

Second, APHIS would not relax its standards for deregulation in order to grant partial deregulation. That is, a partial deregulation would be granted only if APHIS determined that doing so would not significantly impact the human environment. A partial deregulation, like a complete deregulation, would be accompanied by an EA or an EIS, as mandated by NEPA. Draft EISs must be published to elicit public comment. APHIS BRS also publishes all EAs for public comment and addresses comments received, so that public concerns regarding potential environmental impacts of any partial deregulation will be addressed.

4. Issue 4

Are there changes that should be considered relative to environmental review of, and permit conditions for, genetically engineered plants that produce pharmaceutical and industrial compounds?

Genetic engineering technology has advanced to the point where organisms can be developed that produce novel proteins and other substances with biological activity or industrial utility. The gene products made by pharmaceutical and industrial plants may have biological activity or may pose other hazards not associated with proteins and other substances commonly found in the food supply. APHIS will examine this issue in the DEIS, taking into account the current rigorous permit conditions, multiple annual inspections required for these plants, and the nature of the compounds produced by these plants. In practice, any changes in the confinement of plants producing pharmaceutical and industrial compounds would not apply solely to those plants, but to a risk tier that might include those plants.

Alternatives Related to Issue 4

1. No Action—continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds and to allow field testing under very stringent conditions.

2. Continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds. The agency would impose confinement requirements, as appropriate, based on the risk posed by the organism and would consider food safety in setting conditions.

3. Do not allow crops producing substances not intended for food uses to be field tested, that is, these crops could be grown only in contained facilities.

4. Allow field testing only if the crop has no food or feed uses.

5. Allow field testing of food/feed crops producing substances not intended for food uses only if food safety has been addressed.

a. No Action Alternative

Under the No Action alternative, APHIS will continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds and to allow field testing under very stringent conditions. While there is no completely failsafe system, APHIS has drawn on experience with past compliance issues and devised a system of permit conditions that are sufficiently stringent that the field tests pose no significant risk to the environment, including human health.

In APHIS' experience, plants expressing traits with pharmaceutical or industrial purposes are no more likely to escape from field tests or to persist in the environment than plants expressing other traits. It is possible that confinement measures designed to prevent gene flow under normal agronomic circumstances may fail in rare situations, such as extreme weather. A comparison of the environmental impacts of the No Action alternative to the impacts of the other alternatives under consideration involves two questions: (1) What is the likelihood that a particular confinement approach will prevent unanticipated environmental exposure, and; (2) What is the likelihood that unanticipated environmental exposure will result in significant impacts?

b. Action Alternatives

Alternative 2 is much like the No Action alternative, except that the safety of the protein or other substance produced by the transgene could be taken into account. The agency would impose confinement requirements, as appropriate, based on the risk posed by the organism and would consider food safety in setting conditions. In this alternative, if there is a food safety issue and it has not been addressed, an organism may still qualify for outdoor testing, but field test criteria would be made more stringent. These measures could include increased auditing, increased isolation distances, and geographic restrictions. Many other possibilities could be considered. If such restrictions are stringent enough and can be adequately enforced by the agency, this alternative should be highly protective of the environment and human health. Increasing the stringency of protections in which food safety might be at issue should provide added protections over the No Action alternative.

Alternative 3 would contain all pharmaceutical or industrial plants in enclosed facilities, regardless of the risk posed by the organism, and would focus solely on minimizing all potential for unanticipated environmental exposure. Unlike the No Action alternative, which prescribes very stringent confinement conditions for the field testing of pharmaceutical or industrial plants, the full-containment alternative forbids any active releases into the environment. The likelihood that an unanticipated environmental release will result from the No Action alternative is low. However, as acknowledged above, a release could result from an extraordinary event that overcomes the effectiveness of the confinement conditions prescribed by the permit. The likelihood that an environmental release or any environmental impacts will result from the full-containment alternative is extremely low.

Alternatives 4 and 5 rely both on minimizing the likelihood of unintended environmental release and on minimizing the impact to the human environment, should a release occur. Both alternatives implicitly assume that the risk of pharmaceutical and industrial plants will not vary and any unintended releases will have the same consequences for the environment.

In requiring containment for all pharmaceutical or industrial plants with food or feed uses, alternative 4 seeks to eliminate the possibility that a commodity used in human food or actively fed to animals would contain any pharmaceutical or industrial material because these commodity crops would have to be grown under contained conditions if they express pharmaceutical or industrial traits. Under alternative 4, only plants with no food or feed uses would be allowed to be field tested outdoors if they express pharmaceutical or industrial traits. These plants would be field

tested under confinement conditions at least as stringent as those currently in use, although, as discussed earlier, there is the remote possibility that these confinement conditions could be undermined by extraordinary circumstances, resulting in some risk of exposure to these compounds in food or feed, or other environmental exposure.

Alternative 5, like alternative 4, restricts food or feed crops expressing pharmaceutical or industrial traits from being field tested; however, this alternative provides an exception. If the new protein or other substance has been adequately evaluated relative to food safety, then outdoor field tests could occur, even if the plant is a food or feed crop. This alternative recognizes that confinement conditions may fail under extraordinary circumstances. If a failure should occur during the field testing of a food or feed crop producing a pharmaceutical or industrial substance, the commingling of this crop with commodities intended to be used as human food or animal feed would not result in any harm where the substance poses no food safety concerns. While all the alternatives will result in environmental protection, alternative 5 could mitigate the consequences of unintended releases more than alternatives 1, 2, or 4, due to the resolution of food safety questions. Alternative 3 would mitigate the consequences of unintended releases to the greatest extent.

To determine if the field testing of plants can cause environmental impacts without directly affecting humans and animals through food and feed products, analysis would depend on the biological activity of the substance in question, and to what extent the field test could result in significant environmental persistence. APHIS evaluates each plant/trait combination proposed for field testing under permit for its effect on nontarget organisms, including threatened and endangered species (TES). This evaluation includes a determination of the TES likely to be present while the field test is taking place and whether any TES is likely to be exposed to the substance produced by the plant in question. APHIS also evaluates whether the a trait is likely to make the recipient plant invasive or weedy, or likely to make any wild relatives of the recipient plant invasive or weedy, which could impact populations of threatened or endangered plant species. From a biological standpoint, and in APHIS' experience, pharmaceutical or industrial traits do not increase the fitness of the plants in which they are expressed. Therefore, none of the alternatives for revision, as well as the No Action alternative, will have any significant impacts on TES, nor will adopting any of these alternatives result in the substantial establishment of pharmaceutical or industrial traits in wild plant populations.

Although all four of the action alternatives will minimize, by various means, the exposure of humans to substances produced through the field

testing of pharmaceutical or industrial plants, it is not possible to assess accurately the impact on humans from the unanticipated release of these organisms for the following reasons:

- Effects on humans will depend on the pharmaceutical or industrial substance involved, and it is impossible to make general predictions.
- Many pharmaceutical and industrial substances are not toxic.
- Toxic effects may be different for special subpopulations, such as children and people with compromised immune systems.
- Although current science can predict whether a specific protein has the potential to become an allergen, these predictions cannot be made with complete certainty.

However, it is not necessary to know the precise impacts from unanticipated releases of pharmaceutical or industrial plants for APHIS to create a science-based, effective system to regulate these plants safely. APHIS' current focus and its focus under the revised regulations will be the imposition of appropriate confinement measures on field tests of GE plants to minimize impacts on the human environment. To date, there have been no reports of human- or animal-health impacts from the field testing of these plants, and APHIS is not considering any alternatives that propose a less rigorous system than the one currently in place.

Given the above rationale and that the four proposed action alternatives provide additional environmental protections, adoption of any of those alternatives should result, overall, in even fewer and smaller impacts. The adoption of any of the alternatives should result in no significant environmental impacts.

5. Issue 5

The definition of noxious weed in the PPA includes not only plants, but also plant products. Based on that authority, APHIS is considering the regulation of nonviable plant material. Is the regulation of nonviable material appropriate and, if so, in what cases should we regulate?

In some special cases, certain nonviable material originating from a field test (e.g., cell debris, leaves, stems, roots, or seeds) may pose unique types of environmental or human health risks. Currently, APHIS regulates organisms that pose a plant pest risk and does not regulate nonliving material derived from GE organisms. By definition, plant pests are living organisms. However, the noxious weed definition provides authority to regulate nonviable plant products that could "injure or cause damage to crops." Because there may be cases in which potential risks could justify

the regulation of nonviable material, APHIS is considering whether it should regulate nonviable material in those cases.

Alternatives Related to Issue 5

1. No Action—do not regulate nonviable GE material.

2. Regulate nonviable GE plant material in certain circumstances, based on risks posed.

3. Regulate all nonviable GE plant material.

a. No Action Alternative

Currently, APHIS does not regulate nonviable GE material. Nonviable material has been regarded as not posing a significant plant pest risk, but in some circumstances, it might pose other types of environmental risks. The potential for environmental impacts from nonviable material depends on several factors: the amount of transgene expression in the tissue in question, the rate of release of the transgene product from the tissue, the stability of the transgene product, and the biological activity of the transgene product. The noxious weed definition applies not only to living plants but also to plant products if they pose a risk to any of a very wide array of environmental parameters. It may be desirable to use this provision of the Plant Protection Act as the basis for regulating nonviable GE plant material if the material does in fact pose legitimate risks to the human environment.

The technology exists to focus transgene expression in specific tissues, such as seeds, and minimize it in other tissues through the use of tissue-specific promoters. (A promoter is a DNA sequence that enables a gene to be transcribed, that is, enables RNA to be produced from the gene.) Many promoters have been identified that enable transcription only in specific tissues. For example, the production of pharmaceutical compounds in plants is often accomplished through the use of seed-specific promoters. As a result, the pharmaceutical compound is produced only in the seeds of the plant, where it can be easily harvested. However, not every gene construct used in the production of GE organisms employs a tissue-specific promoter; and even when one is used, low levels of transgene expression may occur in other tissues. If these tissues are not harvested, there is a potential for environmental exposure to the transgene product.

Once plant tissues are placed in contact with the soil, the tissues and the substances contained within those tissues begin to break down. Soft tissues will decompose rapidly, while woody tissues may take much

longer. By extension, the chemical contents of soft tissues will tend to enter the environment more quickly than substances contained within woody tissues. In addition, various chemical compounds produced by and stored within plant tissues will also begin to breakdown once those tissues begin to decompose. Some of these substances may breakdown in a matter of minutes; others may take days or weeks. Therefore, if one of these substances is the product of a transgene, its release into the environment will be controlled by the decomposition rate of the plant tissue in which it resides, as well as the rate of breakdown for the substance itself.

A high level of scrutiny might be needed when the transgene product is allergenic, toxic, or has some other physiological effect that would advise against allowing environmental exposure. If the product has none of these properties, less or possibly no scrutiny would be necessary. Even if the transgene product has minimal biological activity, there may be some concern if the compound is very stable once released into the environment or if the nonviable residues left in the environment contained high levels of the compound, resulting in high environmental exposure.

b. Action Alternatives

For most environmental factors discussed in section 1 of this chapter, the question of potential impacts due to nonviable material is inapplicable. For example, APHIS' regulation of nonviable GE plant material is irrelevant to questions of weediness, invasiveness, and gene flow. However, there are potential impacts to the soil, and by extension, groundwater, and soil-dwelling organisms. Most field waste left over from field tests of GE organisms is incorporated into the soil where the field test took place. Less frequently, the waste is collected and devitalized in some way (e.g., via autoclaving or burning), and the residues are then placed in a landfill. Ultimately, the final decomposition of the material takes place in the soil.

As discussed above, depending on a number of factors, this decomposition could result in direct and indirect impacts to soil, soil water, and soil-dwelling organisms. Depending on the transgene product, its buildup in the soil could alter soil chemistry and fertility and could change soil microbial populations. If the product or a substance produced through the transgene product's breakdown is water soluble, it could enter the groundwater and could eventually end up in surface water. Furthermore, if the transgene product decomposes slowly, and if the product is environmentally detrimental, accumulation of the product could result in soil and groundwater contamination.

APHIS' regulation of nonviable GE material could also potentially impact levels of environmental pollution in certain situations. If the transgene product is a toxin or allergen, the unrestricted presence of nonviable plant material containing the product in the environment could increase the opportunities for humans and nontarget organisms to come into contact with the product. However, APHIS restricts the size of permitted field tests involving traits of this type; therefore, this type of exposure would be low.

Impacts on the soil, on environmental pollution, and on allergenic and toxic exposure caused by nonviable GE material might be reduced in specific cases by the regulation of this material. Conversely, in some cases, the regulation may force growers of GE plants under APHIS permit to develop new agronomic practices to collect, dispose of, and monitor this material after harvest and ensure that the material does not remain in the environment. These practices could involve additional equipment use and concomitant energy expenditures as well as other economic costs.

Alternatives 2 and 3 would create regulatory authority over some or all nonviable GE material. Plants for phytoremediation that have accumulated a toxic element or compound might be an example of a special case in which APHIS would want to retain authority over nonviable plant debris until it is properly disposed. In addition to considering the biological characteristics of the debris and how it was generated, APHIS might need to consider if APHIS regulations or permit conditions have been violated. Under normal circumstances, following the APHIS-imposed conditions for field testing, including termination and disposal requirements, would mitigate any potential risks for nonviable material such that it is not necessary to regulate the material. But when violations have occurred, APHIS might want to retain authority over materials that may have been moved and possibly become mixed with commercial goods.

In alternative 2, APHIS would need to either establish clear criteria to enable the regulated community and the public to know which materials were of regulatory concern or evaluate permits on a case-by-case basis to make this determination. In alternative 3, all nonviable material would be deemed regulated and APHIS would determine on a case-by-case basis which items required special permit conditions to minimize environmental and agricultural impacts. The approach in alternative 3 may result in overregulation of materials posing only minimal risk of environmental impacts.

In most cases of GE organisms with which APHIS has experience, there have been no risks posed by nonviable material that has been properly

disposed. APHIS envisions that this will continue to be true for most GE plants. However, as new transgenes are investigated and transgene expression technology advances, the potential exists for environmental impacts to result from the release of nonviable residues from field tests performed under APHIS permit. Given the range of plants released under permit, a simple blanket rule on all nonviable material raises the potential for both over- and under-regulation. If the regulatory scope is too broad, then nonviable materials posing no risk may be unnecessarily regulated, but if the regulatory scope is too narrow, materials posing environmental risks could be excluded from APHIS oversight. A regulation might be crafted which establishes the biological and chemical properties of GE plant debris that would trigger regulation of nonviable material and would also establish that when a permit violation occurs, "the applicant may be held responsible for any measures deemed by the Administrator to be necessary to mitigate adverse environmental impacts resulting from the violation." This approach, regulating only in cases where there is a potential for impacts, might best accommodate the inherent variables and minimize both environmental impacts and regulatory burdens.

6. Issue 6

APHIS is considering establishing a new mechanism involving APHIS, the States, and the producer for commercial production of plants not intended for food or feed in cases where the producer would prefer to develop and extract pharmaceutical and industrial compounds under confinement conditions with governmental oversight, rather than grant nonregulated status. What should be the characteristics of this mechanism?

For organisms that cannot meet the criteria for deregulation, APHIS is considering whether a new type of permitting system would be more appropriate in terms of efficiency and effectiveness than the current system. In addition, there is much public and State interest in these types of plantings and a new mechanism may increase transparency and allow for greater State involvement.

Alternatives Related to Issue 6

1. No Action—continue to authorize field tests of crops not intended for food or feed use under permit. Require application and review of these permits on an annual basis.

2. Allow for special multi-year permits, with ongoing oversight. The new system would maintain these crops under regulation, but APHIS oversight would be exercised in a different manner than under the current system of permits.

a. No Action Alternative

The No Action alternative is to continue to handle all plants under APHIS' permitting system with annual reviews of complete permit packages. In some cases field tests for plants, especially those not intended for food use, are conducted annually, in the same location, with few if any changes to the permit conditions. Each year, therefore, APHIS reviews a full permit application for a field test that is essentially the same as the previous year's application. These reviews ensure a high level of protection to a wide array of environmental parameters, but it is an inefficient process for both the agency and the applicant.

b. Action Alternatives

For alternative 2, because of the controls that can be put into place, the adoption of a new alternative system should not be different than current permits with respect to the types or amount of environmental impacts. Any new system put in place would merely create a continuing enforcement process for permit conditions that APHIS has already approved. APHIS would not compromise any of its technical oversight because changes to the field testing would need approval prior to the changes occurring. Nor would there be any compromise of the agency's enforcement authority. If necessary, a NEPA-compliant EA, or EIS if appropriate, would be prepared to determine if indirect or cumulative environmental impacts could result from permitting field tests to continue for multiple years.

7. Issue 7

The current regulations have no provision for the low-level presence of regulated articles in commercial crops, food, feed, or seed of GE plant material that has not completed the required regulatory processes.[32] Should low-level occurrence of a regulated article be exempted from regulation?

As with traditional plant breeding, large scale annual field testing of GE crops that have not completed all applicable reviews inevitably results in materials from these trials occasionally being detected at low levels in commercial commodities and seeds. Current regulations do not expressly allow for any such occurrence, though experience continues to show that such occurrences can occur. In a 2002 OSTP notice,[33] APHIS committed to conducting a risk-based regulatory program that minimizes the

[32] In the NOI, the term *adventitious presence* was used to refer to the "intermittent low levels of biotechnology-derived genes and gene products occurring in commerce that have not gone through all applicable regulatory reviews." However, APHIS realizes that this term means different things to various interests around the world; hence, we will avoid its use elsewhere in the main body of the EIS.

[33] 67 FR 50577

occurrence of these materials and includes safety criteria under which these materials would be allowed at low levels in commercial commodities and seeds. Though the 2002 OSTP notice uses the term "allowable," the agency currently prefers "non-actionable" as it better connotes that such materials are still regulated and any introductions not in accordance with the regulations or permit conditions are unlawful. Non-actionable means that based on safety considerations, agency action to restrict movement or otherwise prevent environmental introduction is not necessary.

Alternatives Related to Issue 7

1. No Action—allow field testing to continue using current confinement strategies to reduce the likelihood of regulated articles occurring in commercial commodities or seeds.

2. Establish criteria under which occurrence of regulated articles would be allowable, that is, considered not-actionable by APHIS. Do not allow field testing of crops that do not meet all of criteria, including addressing food safety issues if applicable (i.e., if the GE plant is a food crop).

3. Establish criteria under which occurrence of regulated articles would be allowable, that is, considered not-actionable by APHIS. Allow field testing and impose confinement strategies based on whether a plant meets the criteria.

4. Impose a very strict confinement regime on all field tests, as is currently done for pharmaceutical and industrial crops that would further reduce the likelihood of regulated articles occurring in commercial commodities or seeds.

This discussion is limited to low-levels of biotechnology-derived genes and gene products occurring in commerce that have not completed all applicable regulatory reviews. This occurrence can originate from various activities and sources, one of which is the field testing of GE crops under development. It can also be present in imports, originating from foreign field tests of unapproved products or from products approved in another country, but not in the United States.

a. No Action Alternative

While some human-health safeguards are built into the system, there is no consideration of whether the protein or other substance has been evaluated for key food safety issues under the current system for field testing. In

addition, because decisions are made case-by-case, there is poor transparency with respect to how these types of incidents are handled. Many GE plants under development express common proteins that are unlikely to pose an environmental or food safety risk; however, such plants are not always reviewed for food safety prior to or during the field testing stage. Still many of these proteins are identical to those that have been reviewed for plant pest potential at APHIS and may have completed the consultation process at FDA or been reviewed for safety at EPA. Both of these agencies either have mechanisms in place or are in the process of establishing mechanisms to provide a food-safety consultation or review of the newly expressed substance early in the field testing process. The PPA explicitly gives APHIS responsibility under the noxious weed provision to consider risks to public health; however, APHIS is not currently using this provision in its regulations.

Under the No Action alternative, APHIS would continue to adjust confinement strategies based on the potential for environmental impacts and continue to handle incidents on a case-by-case basis. APHIS anticipates that the rigorous confinement conditions it imposes will continue to ensure that regulated articles very rarely occur in commercial commodities or seeds. In addition, APHIS' response to such incidents has been aggressive, including large monetary penalties and actions to hold and destroy affected commodities. Remedial measures in those instances have resulted in no significant environmental impacts.

b. Action Alternatives

A general discussion about the occurrence of regulated materials in commercial commodities and seeds is necessary before presentation of new alternatives for dealing with it. APHIS believes it will be appropriate under the new regulations to consider key food safety issues of toxicity and allergenicity for most new proteins or other substances expressed when imposing confinement regimes on the field testing of GE plants in order to minimize public health risk in the unlikely event that material escapes confinement. Plants that are not weedy and that are engineered with agronomic traits with which the agency is familiar are often authorized for field testing using the notification procedure. The eligibility requirements for notification are preset and listed in the regulations at 7 CFR § 340.3. The vast majority of field-tested GE plants are authorized using the notification process. Confinement of such plants is based on long-established industry standards for producing foundation seed lines, those of the highest genetic purity. However, this type of confinement could conceivably result in material from regulated field tests being found in commercial seeds and commodities.

APHIS has taken many steps in recent years to increase the stringency of confinement measures and expand APHIS oversight for plants that do not qualify under notification. For example, permit requirements for field testing of plants with genes producing pharmaceutical or industrial compounds are among the most stringent, reflecting, among other things, the agency's lack of familiarity with the traits in these types of plants. Based on these rigorous permit requirements, APHIS does not expect materials from these types of field tests to occur accidentally in commercial products.

Consistent with the Office of Science and Technology Policy's *Federal Register* announcement of August 2002, there are two objectives in APHIS' approach. The first is to establish safety criteria under which such occurrences would be non-actionable. The second is to regulate materials that do not meet these criteria in such a way that it is highly unlikely that they would ever occur in commercial commodities or seeds. As mentioned previously, the agency has made significant progress in fulfilling the second objective, namely regulating certain GE plants (e.g., those producing pharmaceutical or industrial compounds) in such a way as to ensure that no regulated material originating from such plants in commercial goods. The section of the DEIS in this chapter regarding crops expressing genes for pharmaceutical or industrial use deals specifically with the confinement of pharmaceutical plants. APHIS will continue to refine its regulatory approach for handling these types of plants to reflect the latest science and its accrued experience.

This section of the DEIS will focus on the first objective, to establish the safety criteria under which such occurrences would be non-actionable. Though these safety criteria relate to the tiered permitting system proposed for field testing, they will also be used to determine whether the presence of a regulated article would be non-actionable. It is important to distinguish between commercial commodities containing low levels of a regulated material, and the regulated material when it occurs alone. "Non-actionable" in this context means that the commercial commodity containing the low level of otherwise regulated material would not be treated as a regulated article; the commodity could be moved and planted without the need for APHIS biotechnology permits covering the otherwise regulated material. It does not mean that any regulated article would be allowed to be released in any unauthorized fashion. Any violation of regulations or permit conditions could result in compliance actions against the violator regardless of whether the resultant presence in commercial commodities or seeds was considered actionable by the agency and required remediation. The desired outcome is to assure the public, including domestic and foreign markets, that safety issues have been

addressed for regulated materials which, on rare occasions, are detected in commercial products.

The tiered permitting system for plants that APHIS is considering is central to understanding the four alternatives described below. Currently, GE plants released under notification must meet APHIS eligibility criteria which ensure that they are unlikely to pose a plant pest risk (see chapter 2 for the list of criteria). These criteria address many of the environmental risks that could be posed by occasional low-level occurrence of these types of plants. Previously in this DEIS, under issue 2 of this section, an example was presented of possible eligibility criteria for Type 1 permits. These criteria were derived by modifying the existing eligibility criteria for notification to include additional weediness considerations and adding a new seventh criterion requiring that food safety be addressed for food crops. It is envisioned that the criteria that would be finalized in the new regulations for Type 1 permits would also be the basis for non-actionable presence of regulated articles in commercial commodities and seeds.[34]

Proposed Criteria Under Which Presence of Regulated Articles in Commodities and Seeds Would Be Considered Non-actionable by APHIS:

1. The regulated article is any plant species that is not on the Federal list of noxious weeds in regulations at 7 CFR part 360 under the PPA (7 U.S.C. § 7712), and, when being considered for field testing in the environment, the regulated article is not expected to establish and propagate outside of the managed ecosystem. Examples of organisms that might not qualify for this reason are open-pollinated turf and forage grasses, forest trees, and aquatic plants.

2. The genetic material is introduced using a method that has been demonstrated to result in integration of the new sequences into the plant genome, as defined in 7 CFR § 340.1.

3. The function of the introduced genetic material is known and its expression in the regulated article does not result in plant disease.

4. The introduced genetic material does not:
   - Cause the production of an infectious entity, or

[34] The only difference between the requirements for a Type 1 permit and the criteria for nonactionable presence is that the 10-acre limit in the permit requirements is not applicable to nonactionable presence, meaning that the presence of any such material that is found in commercial commodities of seed, originating from either domestic or foreign field tests, should have had protein safety issues addressed.

- Encode substances that are known or likely to be toxic to nontarget organisms known or likely to feed or live on the plant species, or
- Encode substances with whose function APHIS is unfamiliar (e.g. substances intended for pharmaceutical or industrial use).

5. To ensure that the introduced genetic sequences do not pose a significant risk of the creation of any new plant virus, plant virus-derived sequences must be:
   - Noncoding regulatory sequences of known function, or
   - Sense or antisense genetic constructs derived from viral genes from plant viruses that are prevalent and endemic in the area where the introduction will occur and that infect plants of the same host species and that do not encode a functional noncapsid gene product responsible for cell-to-cell movement of the virus.

6. The plant has not been engineered to contain the following genetic material from animal or human pathogens:
   - Any nucleic acid sequence derived from an animal or human virus, or
   - Coding sequences whose products are known or likely causal agents of disease in animals or humans.

7. If the GE plant is a food crop, it either has a pesticide tolerance[35] from EPA or key food safety issues of the new protein or other substance have been addressed.

8. The plant does not have sexually compatible relatives that are threatened or endangered.

Alternative 2 would forbid the field testing of GE organisms whose transgene products do not meet safety criteria to be established for Type 1 permits in the tiered permitting system described earlier. If only such GE organisms are field-tested, then the detection of their transgene products in commercial seeds and commodities should not have significant impacts and would be non-actionable. However, allowing field testing only of this type could unnecessarily impede research and prevent the development of beneficial products in the future. For example, under this system it might not be feasible to test and develop plants engineered for pharmaceutical use, industrial use, or for phytoremediation if they cannot meet the safety criteria. In addition, the agency believes these types of GE plants can be safely field tested even though they do not meet the safety criteria for being non-actionable should they occur in commodities or seeds. Safety is

[35] See EPA's "Regulations Under the Federal Insecticide, Fungicide, and Rodenticide Act for Plant-Incorporated Protectants" at http://www.epa.gov/pesticides/biopesticides/pips/pip_rule.pdf .

assured by imposing highly stringent confinement conditions so as to minimize the probability of such an incident, and thereby, minimizing risks of environmental impacts. The agency currently draws upon almost 20 years of experience and the best available science in order to minimize the probability of gene flow from these types of experiments; therefore, the constraints on field testing created by this alternative may not be justified based on risk. These types of field tests have not resulted in reports of environmental harm.

Alternative 3 also incorporates the same safety criteria used in the Type 1 permit as the basis for whether a given regulated article would be considered non-actionable if detected in commercial seeds or commodities. However this alternative differs from alternative 2 in that in this alternative field testing of GE plants not meeting the criteria is allowed, but more stringent confinement measures are applied. Though this alternative is highly compatible with the tiered permitting system and described in those terms, it is in actuality independent and could be adopted even if the tiered permitting system is not adopted. As noted, the majority of plants field tested would likely fall under Type 1 permit which would require similar confinement strategies to those used for notification under the current system. Given the type of confinement and the large numbers of tests that are anticipated to be conducted in this way, it is possible that on occasion there will be gene flow in the form of pollen drift or commingling such that material derived from these tests may occur in commodities or seeds. If this happens, the criteria above should assure that the safety of the material has been addressed and therefore, the occurrence would be non-actionable. Under the proposed tiered approach for permits, testing of GE plants that have not been reviewed for food safety would be limited to 10 cumulative acres annually, so that environmental exposure and the opportunities for significant interaction with the environment or commercial production channels would be very low. The food safety review criterion would either have to be met before the test acreage was increased or else the plant would have to be moved to a more stringent permit type.

In summary, the confinement measures that would be imposed on field tests that are most likely to give rise to the presence of regulated material in commercial commodities or seeds should provide environmental protection that is as effective as the status quo (alternative 1, No Action) and only slightly less than alternatives 2 and 4. GE plants that did not meet the safety criteria could also be field-tested under this alternative, but under very strict confinement requirements, such that the chance of detection in commodities and seed, as well as impacts on the human environment, would not be significant. As discussed earlier, the agency has considerable experience in overseeing both types of experiments and

regulating them in a way that assures safety. As a variation on this alternative, it would also be possible to use criteria such as those outlined for a Type 1 permit for GE plants as the basis for actions on nonregulated materials in commercial seed and commodities if APHIS elects not to adopt a tiered permitting system.

Alternative 4 focuses on the prevention of gene flow and proposes the imposition of much stricter permit conditions, including confinement measures on all field tests regardless of which safety criteria are met. Under this alternative, all permitted field tests would be performed under conditions equivalent to those currently employed for pharmaceutical or industrial GE plants—conditions that have been effective in preventing gene flow. By reducing the potential for the unintended movement of genes, the likelihood of detecting these genes or their products in commercial seed and commodities should similarly be reduced. Their occurrence would not be anticipated but would be actionable in the unlikely event that they were detected. This alternative may increase costs and other burdens on the future development of GE plants for general agricultural use. In addition, this alternative would increase the time required to review permit applications and to devise appropriate confinement measures for each proposed field test. It is also likely that the number of permits issued each year would be reduced. This alternative would result in the lowest potential for the presence of regulated materials from domestic field tests in commercial commodities and seeds, short of not allowing any field tests at all. However, safety may be only incrementally more protective if at all, than that afforded by a system that effectively differentiates risks during field testing and then imposes the very high confinement regime only on those GE plants that might give rise to a safety concern if detected elsewhere.

A separate but closely related issue is that of coexistence. The term co-existence refers to the ability of a farmer to use a particular type of crop production, regardless of the production methods adopted by his or her neighbors.[36] As GE crops continue to be adopted, it is increasingly likely that farms on which GE crops are grown will be situated near farms where conventional or organic production is practiced. With the juxtaposition of various types of agricultural production, there exists the possibility for inadvertent commingling of GE commodities with conventional or organically produced crops and vice versa. In addition, genes may flow from fields under one type of production to fields managed under another type. Commingling and gene flow could affect the value of any crop—

[36] See, for example, the Commission recommendation of 23 July 2003 on guidelines for the development of national strategies and best practices to ensure the co-existence of genetically modified crops with conventional and organic farming. Commission of the European Communities. Brussels.

GE, conventional, or organic—and there are ongoing research efforts to investigate successful methods for minimizing these effects (Messeguer and Melé, 2006).

The National Organic Program (NOP) is administered by USDA's Agricultural Marketing Service (AMS). Organic production operations must develop and maintain an organic production system plan approved by their accredited certifying agent in order to obtain certification. Organic certification of a production or handling operation is a process claim, not a product claim. Organic certification involves oversight by an accredited certifying agent of the materials and practices used to produce or handle an organic agricultural product. Oversight by a certifying agent includes an annual review of the certified operation's organic system plan and on-site inspections of the certified operation and its records.

The organic system plan enables the production operation to achieve and document compliance with the National Organic Standards, including the prohibition on the use of excluded methods. Excluded methods include a variety of methods used to genetically modify organisms or influence their growth and development by means that are not possible under natural conditions or processes. Although the National Organic Standards prohibit the use of excluded methods, they do not require testing of inputs or products for the presence of excluded methods, unless a certifying agent has reasonable suspicion that a prohibited substance or excluded method was used. The presence of a detectable residue of a product of excluded methods alone does not necessarily constitute a violation of the National Organic Standards.

The alternatives proposed here have no impact on the National Organic Standards, nor does the adoption of any of the alternatives have any affect on an organic producer's ability to attain NOP certification. However, the adoption of any of the alternatives other than the No Action alternative may provide additional safeguards to the organic industry and agriculture at large. A full discussion of potential economic and social impacts on organic and other non-GE agricultural products appears later in this chapter.

8. Issue 8

Should APHIS provide expedited review or exemption from review for certain low-risk, imported GE commodities intended for food, feed, or processing that have received all necessary regulatory approvals in their country-of-origin and are not intended for propagation in the United States?

APHIS anticipates an increasing number of requests to import regulated GE organisms that are not intended for propagation, such as organisms

that are intended for direct use as food, feed, or for processing. The current regulatory system was designed to handle such requests using permits and notifications. However, in anticipation of this increase, APHIS' goal is to design an efficient system that protects U.S. agriculture and human health without erecting unnecessary trade barriers. To that end, the agency has evaluated several different alternatives.

Alternatives Related to Issue 8

1. No Action—continue to evaluate commodity importation requests on a case-by-case basis.

2. Establish criteria that will be applied to determine the appropriate level of risk assessment for imported GE commodities. This alternative could include a decision to exempt certain products or to allow importation under conditions that minimize environmental release.

3. Disallow importation of any commodity pending full APHIS approval for deregulation.

4. Expedited review of product from a foreign country that has evaluated the safety of the product and approved it for unconfined environmental release.

5. Expedited review of a product from a foreign country that has evaluated the safety of the product and approved it for unconfined environmental release using a review process equivalent to APHIS'.

a. No Action Alternative

APHIS anticipates an increased volume of imported GE commodities with new plant/trait combinations, and the current process may not be able to address the needs of international trade efficiently while providing adequate environmental protection. Other nations undoubtedly have similar issues when they import from the United States commodities that have completed all applicable reviews here but not in the importing country. It is desirable for U.S. regulatory systems affecting international trade to foster harmonization with analogous systems employed by foreign nations. A lack of harmonization could result in the imposition of trade barriers, making it difficult for GE commodity products to reach markets.

The No Action alternative will continue to treat imported commodities as "regulated articles" if they are genetically engineered and have not been

deregulated by APHIS. Importation of regulated GE commodities requires either a notification or a permit and may be subject to a risk assessment. Currently, the importation of GE commodities not deregulated in the United States happens only rarely because, until recently, very few foreign nations were producing GE crops of a type not also developed for use in the United States. In a very few cases, the agency has determined that due to the nature and handling of the importation, the imported GE organisms do not fit the definition of a regulated article.

The principal risk from importing regulated GE commodities for food, feed, or processing would be inadvertent spillage into the environment, establishment, and subsequent harm to the environment. This series of events may be a very low likelihood in most instances, but would vary according to the plant, trait, and handling procedures. The current policy is highly protective of the environment, but is inefficient in the use of agency resources. Also, regulatory burdens may be excessive for commodities bound for food, feed, and processing because of their lower environmental risk. In cases where the commodity is highly unlikely to establish or persist, either due to its biological nature or its handling, there will be a very low likelihood of environmental impact.

b. Action Alternatives

The international situation is changing as foreign nations develop their own agricultural biotechnology research programs and begin to release products into the market that have undergone a risk analysis process under a foreign nation's regulatory authority. APHIS anticipates a growing number of requests for the importation of GE commodity shipments and has considered a number of alternatives to the current practice of preparing case-by-case risk assessments to address increased import traffic. It is a goal for the preferred alternative to protect the human environment of the United States without becoming a trade barrier, either to imports of foreign commodities or to exports of domestic GE commodities.

Alternative 2 for dealing with the importation of GE commodities is to create criteria that specify which commodities will be exempted from APHIS review. These criteria would take into account several relevant factors such as a pathway analysis, including the final intended use of the commodity, that is, whether the commodity would be processed or used for food or animal feed; whether the protein or other substance has been adequately evaluated relative to food safety; and whether the commodity is nonpropagable, for example, bananas or polished white rice. Before exempting a GE commodity, APHIS would require that the importer

certify that the commodity complies with all appropriate criteria and verify that the commodity will be used only for processing, food, or animal feed.

If the criteria for exemption are not met, the commodity could still be imported but only under the terms of an import permit. The terms of the permit would specify conditions designed to prevent the dissemination and environmental persistence of the GE commodity. Appropriate permit conditions may include shipping container requirements, pathway analysis, proper handling conditions, auditing practices, and compliance enforcement. These permits would be analogous to permits currently issued by APHIS for the interstate movement of regulated articles.

The exemption criteria proposed above should ensure that exempted GE commodities would not result in significant environmental impacts, even if an environmental release should accidentally occur. For the near future, only a fraction of GE commodities proposed for importation into the United States will comply with all the criteria and qualify for an exemption. Non-exempted commodities could be imported under a permit designed to minimize environmental impacts. Based on APHIS' experience issuing movement permits, the agency is confident that import permits can be designed in such a way so that no significant adverse environmental impacts occur.

Alternative 3 is for APHIS to treat every importation request as a petition for deregulation. No importation of a GE commodity, regardless of biology and intended use, would be permitted unless the commodity is deregulated for all uses. The importer would be forced to provide the full data set necessary under 7 CFR § 340.6, regardless of the data collected and evaluated by the exporting nation. As discussed elsewhere in this document, APHIS' current deregulation process has been protective of the environment and should continue to result in no significant environmental impacts. Therefore, extending the scope of deregulation to all importation requests for commodities to be used for food, feed, or processing should, by the same token, have no significant environmental impacts.

The costs of this alternative are primarily in agency resources and applicant regulatory burdens. As the number of import requests increase, APHIS anticipates an increase in the amount of resources devoted to the consideration of petitions for deregulated importation, even when the commodity in question has already been reviewed by the exporting nation. This duplication of effort will likely impede the number of commodity imports that can be authorized. Also, in selecting this alternative, APHIS is effectively ignoring the regulatory authority and risk assessments of the exporting nation. There is a risk that other nations may respond in kind and give no credence to the analyses prepared by APHIS, which would

otherwise be used by United States producers hoping to export GE commodities to other countries, potentially resulting in export barriers for U.S. producers.

Alternative 4 would be to have an expedited review of any commodity that had been reviewed by the exporting country. While this would be expected to decrease risks in many cases, it may be erroneous to assume that evaluations in all countries would be adequate to assure that there would be no negative impacts in the United States. This approach would decrease workload, but would likely have a greater potential for environmental impacts than all other alternatives given uncertainty in the qualities of the reviews. The approach in alternative 4 may differ from that used by other APHIS programs regulating non-GE organisms.

Alternative 5 would create an expedited APHIS review for GE commodities that have undergone a risk assessment in the country of origin equivalent to the one performed by APHIS for GE organisms prior to their deregulation in the United States. The goal of this alternative is to ensure that an imported GE commodity has received a complete safety and environmental review without APHIS duplicating the efforts of foreign agencies that have comparable expertise and equivalent regulatory processes. This approach fosters mutual respect for each nation's regulatory authority, facilitates data sharing, and reduces the chance that trade barriers will be raised unnecessarily. However, APHIS' review of a particular GE commodity would not end with the mere acknowledgment that the exporting nation has performed a risk assessment. No two countries could be expected to review GE organisms in the same way: regulatory authorities will differ, data requirements will vary, environmental conditions may be different, and the depth of the analysis may not be comparable. Therefore, APHIS' review of a particular importation request will depend on the thoroughness of the analysis performed by the exporting nation.

APHIS could deal with different risk-assessment processes in two ways. First, APHIS could review a nation's assessment process and then determine that it is as likely as APHIS' process to adequately verify that the GE commodity poses no greater environmental risk in the United States than the conventionally bred version of the commodity. Once a nation's assessment process has been deemed equivalent to APHIS', risk assessments produced by that nation would not require a full APHIS review. Alternatively, APHIS could evaluate each risk assessment produced by a given exporting nation on a case-by-case basis to verify that a thorough evaluation has been done. In either case, a finding by APHIS that the assessment did not meet agency requirements would result in the import request being denied.

The chief benefit to this alternative is in reducing the expenditure of agency resources while at the same time providing leadership to the international community in the use of science-based approaches to address the risks of GE organisms. In addition, by granting validity to the assessments produced by foreign nations, when appropriate, APHIS minimizes the development of arbitrary trade barriers. Because the endpoint for each analysis is the determination that the GE commodity has received as thorough an analysis as if APHIS itself had performed it in its entirety, based on APHIS' experience with the deregulation of more than 70 GE crop varieties, this alternative should not result in significant environmental impacts.

9. Issue 9

Currently, genetically engineered *Arabidopsis* spp. are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. Should the movement of genetically engineered *Arabidopsis* spp. or other GE organisms be exempted from movement restriction?

Currently, genetically engineered *Arabidopsis* spp. and a few other organisms are exempt from interstate movement restrictions under 7 CFR 340.2 because they are well understood and extensively used in research. The agency is considering whether to expand the current exemption from interstate movement restrictions to other well-studied, low-risk, GE research organisms. Such a change would create a consistent, risk based approach to organisms with similar risk profiles.

Alternatives Related to Issue 9

1. No Action—retain the current list in 7 CFR § 340.2(b).

2. Exempt a class of GE plants or organisms that are well-studied and present little or not environmental risk from permit requirements for interstate movement as is currently done for *Arabidopsis*.

3. Create a process to apply for an exemption for a particular species.

a. No Action Alternative

The No Action alternative is to retain only the items currently listed in 7 CFR § 340.2 as being exempted from the requirements of an interstate movement permit. Certain types of organisms, including those currently exempted, are inherently lower in risk than others. In addition, shipping organisms interstate in enclosed containers is a low-risk activity that is very unlikely to result in release, establishment, or harm. Hence, the current system of limited exemptions is highly protective of the human

environment has not resulted in environmental impacts and is not likely to result in future environmental impacts.

b. Action Alternatives

Alternative 2 would be to exempt the low-risk organisms in Type 1 permits from the requirements of a permit or notification for interstate movement. These same criteria could be applied for exemption under this issue regardless of whether the tiered table was adopted. Please see the analysis of the tiered permitting system under issue 2, discussed earlier in this same section and chapter. The eligibility criteria for a Type 1 permit under the proposed system are very similar to those for notification under the current system.

If a multitiered system is not adopted in the revised regulations, APHIS could select alternative 3, which is to create a process with appropriate criteria independent of the tiered system that describes GE plants to be exempted from the requirement of any interstate movement permits.

The two alternatives described above should each provide protections equal to the present system if the criteria are carefully considered. Under either alternative, researchers would still be bound under the regulations to transport using containers that meet APHIS standards for safety. In addition, APHIS may require that they keep or submit records of what is transported. The difference from the current system is that they would not have to apply for or wait for receipt of a permit.

10. Issue 10

What environmental considerations should be evaluated if APHIS were to move from prescriptive container requirements for shipment of GE organisms to performance-based container requirements, supplemented with guidance on ways to meet the performance standards?

APHIS regulations prescribe the use of several types of packaging to prevent the escape, dissemination, and environmental persistence of GE organisms. However, based on APHIS' experience there are other types of containers that can be used to safely move GE organisms. APHIS often grants applicants a variance to use a different container to transport a GE organism in a way other than prescribed by the regulations but reviewing these requests takes agency resources. APHIS is considering alternatives that will reduce the need for variances but still facilitate the safe movement of GE organisms.

APHIS is considering whether to move from prescriptive packaging requirements for the shipment of GE organisms to performance-based container requirements.

Alternatives Related to Issue 10

1. No Action—retain current list of approved containers and issue variances when necessary.

2. Switch to performance-based standards for all shipping containers.

3. Expand current list of approved containers and issue variances when necessary.

a. No Action Alternative

Under the current system, several types of transport containers have been prescribed in APHIS regulations to prevent the escape, dissemination, and environmental persistence of GE organisms. In cases where specific shipments of a GE organism cannot be accomplished using one of the specified containers, the applicant may propose to APHIS an alternative container and request a variance from APHIS to use that container under the terms of a specific permit. The proposed variant container is evaluated by APHIS to verify that it will effectively prevent an environmental release of the GE organism in question. No blanket variances are issued. Although the container is nonstandard, its use must result in the same endpoint, namely, no release of GE organisms into the environment.

Container failure, in APHIS' experience, has not been a source of significant environmental releases or impacts. Failures resulting in the need for an APHIS investigation and compliance enforcement are rare, occurring less than once per year. Spills, when they do occur, are likely to occur indoors, inside vehicles, or in other contained spaces where the spills will be readily identified and easily cleaned up. Therefore, these rare events have not resulted in the dissemination or persistent environmental establishment of regulated articles. Thus, there are no significant environmental impacts to the No Action alternative.

b. Action Alternatives

If APHIS elects alternative 2, to establish performance standards for shipping containers, many permit applicants would continue to select their shipping containers from the current list of approved containers that would be provided to applicants through guidance documents. For those applicants who opt to design new containers in compliance with the

performance standards, APHIS anticipates that as long as the containers meet the standards, their use should not result in the dissemination or persistent environmental establishment of regulated articles. Therefore, it is expected that to switch to performance-based standards for shipping containers would pose no significant environmental impacts.

If APHIS elects alternative 3, to add to the list of prescribed containers in the regulations, the newly added containers would be designed with the same fundamental goal of the original containers, to prevent the accidental environmental release of regulated articles. Variances to these prescribed container types would still be evaluated by APHIS if requested, requiring agency resources, but APHIS would not expect any new environmental impacts from this alternative, when compared to the No Action alternative.

D. The Proposed Action: Preliminary Determination

With respect to the issues and associated alternatives, APHIS has made a preliminary determination that action should be taken. APHIS has also made a preliminary decision that the action will require revision of the APHIS regulations at 7 CFR part 340. Regulatory revisions under consideration are based on agency experience and utilize new provisions of the PPA of 2000. They have the potential to increase effectiveness, efficiency, and transparency and decrease negative environmental impacts. They reflect the current thinking and should not be considered as final nor as a rule proposal.

1. Issue 1

Scope of Regulatory Oversight

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Expand the scope of what is regulated by adding considerations of noxious weed risk and regulating GE biological control organisms in addition to evaluating plant pest risks, and use genetic transformation as the trigger for regulation. Continue to regulate event-by-event."

This alternative would eliminate potential gaps that may occur as genetic engineering technologies continue to advance. Because the expanded scope would require APHIS to evaluate a wider array of potential risks, the risk of introducing potentially harmful GEOs would be reduced, and the risk of environmental impacts resulting from the introductions would also be reduced. Therefore, the adoption of this alternative should result in a reduced potential for significant adverse impacts to the environment as compared to the current system. Neither regulating by transformation "event" nor regulating by trait should increase the potential for impacts to

the natural or physical environment or any interrelated economic or social impacts.

In addition, APHIS has made a preliminary determination that alternative 4—"Exclude specific classes of highly familiar organisms and highly domesticated, nonweedy crop plants and also create a mechanism to exclude additional organisms from the definition of regulated article after a safety review"—which could be used in conjunction with alternative 2, will also be included in the preferred alternative because it will allow APHIS to exclude classes of organisms which do not pose a significant risk and, thereby, allow resources to be focused on those organisms which have a greater potential risk, This will reduce unnecessary regulatory burdens for the agency and developers.

Because the scope of organisms being regulated is being broadened, it is appropriate to have a way to exclude classes of organisms which do not pose a significant risk. This allows resources to be focused on those organisms which have a greater potential risk and reduces unnecessary regulatory burdens for the agency and developers. By excluding certain GE organisms from regulation and thereby allowing an increasing number of GE organisms to be grown, the proposed exclusion provision may increase the potential for gene flow from GE crops to non-GE crops.

2. Issue 2

Providing transparency and predictability within a risk based permitting system

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 4—"Establish a tiered permitting system for plants based on newly devised criteria and evaluate permit applications for field tests of nonplant organisms on a case-by-case basis."

The criteria will be more transparent, allowing developers and the public to see that organisms are to be regulated based on risk and familiarity. APHIS believes that this system would be as protective of the environment as the current system because the agency would continue to provide appropriate oversight to ensure that all GEOs released into the environment are safe, and would continue to perform NEPA compliant environmental analyses when a proposal to introduce a GEO raised new issues with which APHIS lacked familiarity.

3. Issue 3

Granting nonregulated status

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Develop appropriate

safety criteria and procedures through which plants can be either (1) fully removed from agency oversight or (2) retained under some degree of oversight as necessary to mitigate any minor risks."

The added flexibility of being able to retain some oversight may be useful for some types of GE organisms that might be developed in the future. Adding this flexibility does not diminish the agency's ability to fully deregulate GE organisms as it does now or to deny a request for deregulation altogether. Retention of oversight might be handled in one of two ways: (1) use the current system and deregulate "in part," or (2) revise the regulations to create a new mechanism such that regulatory oversight is retained for those cases where it is warranted. The added flexibility should not diminish protection of the environment relative to the current system.

4. Issue 4

Permit conditions for genetically engineered plants that produce pharmaceutical and industrial compounds

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Continue to allow food and feed crops to be used for the production of pharmaceutical and industrial compounds. The agency would impose confinement requirements, as appropriate, based on the risk posed by the organism and would consider food safety in setting conditions."

Based on previous experience in field testing of plants producing these compounds, the use of highly stringent confinement measures can be used effectively to protect the environment from significant impact. Consideration of food safety, specifically whether the protein or other substance has been characterized for allergenicity or toxicity to humans, will further enhance the risk-basis of the regulations with respect to safety to humans.

5. Issue 5

Nonviable GE material

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Regulate nonviable GE plant material in certain circumstances, based on the risks posed."

For most GE plants, the resulting nonviable material from field testing will not pose a significant risk to the environment. However, the agency can envision special cases where the nature of the material might be such that it would require oversight to ensure safe handling and disposal. In addition, the agency may wish to assert authority over nonviable material

when there is a need for remediation due to a violation of permit conditions or regulations.

6. Issue 6

Oversight of plants (e.g. pharmaceutical plants) that might be produced commercially under permit

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Allow for special multi-year permits, with ongoing oversight. The new system would maintain these crops under regulation, but APHIS oversight would be exercised in a different manner than under the current system of permits."

The new system could be just as protective of the environment as the current system, but in a manner that is more efficient than the current system. This could be accomplished initially by giving an application full APHIS review, including standard operating procedures (SOPs) for repetitive activities. Any changes to the original permit application or approved SOPs would have to be submitted to APHIS for approval prior to implementation. These sites would still be subject to inspection and would also rely on auditing to ensure activities are conducted according to approved permit conditions and SOPs. APHIS does not anticipate that these proposed commercialization permits would be granted frequently. As with any regulated article, APHIS would continue to require that any permitted field trials, including those under a multi-year permit, must always be performed at an appropriate isolation distance to maintain confinement and minimize gene flow or other potential impacts on any type of surrounding agriculture.

7. Issue 7

Low-level GE presence

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 3—"Establish criteria under which occurrence of regulated articles would be allowable, that is, considered not-actionable by APHIS. Allow field testing and impose confinement strategies based on whether a plant meets the criteria."

APHIS and the U.S. government have been aware for some time that the occasional detection of regulated material in commercial crops as seeds is a scientific reality as a result of field tests conducted under confinement conditions appropriate for notifications. This is due to cross-pollination and also, commingling from shared equipment and facilities. In addition, new incidents will inevitably result from the importation of seeds and commodities from countries where such material has been fully approved but has not completed all U.S. reviews. In the majority of cases, this low-level occurrence of regulated articles will be of minimal risk, and this

should be accounted for in any regulatory scheme since oversight should be commensurate with risk. Our analysis indicates that material meeting the safety-based criteria of alternative 3 will not pose a risk for significant environmental impact and therefore, its occurrence can be considered nonactionable by the agency.

8. Issue 8

Importation of GE commodities not intended for propagation

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Establish criteria that will be applied to determine the appropriate level of risk assessment for imported GE commodities. This alternative could include a decision to exempt certain organisms or to allow importation under conditions that minimize environmental release."

The proposed exemption criteria should ensure that exempted GE commodities would not result in significant environmental impacts, even if an environmental release should accidentally occur.

9. Issue 9

Interstate movement of well-studied, low risk organisms

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—" Exempt a class of GE plants or organisms that are well-studied and present little or not environmental risk from permit requirements for interstate movement as is currently done for *Arabidopsis.*"

An analysis of the impacts indicates that expansion of the exempted list to other well-studied research organisms would present little or no risk of significant environmental impact. This expansion could offer substantial regulatory relief to small startup companies, public institutions, and academic researchers whose resources are often strained to comply with regulations for GE organisms.

10. Issue 10

Shipping standards

To address this issue, APHIS has made a preliminary determination that the preferred alternative will include alternative 2—"Switch to performance-based standards for all shipping containers."

Having performance-based standards for shipping containers would obviate the need for variances and would, therefore, reduce the burden on applicants, as well as increase the efficient use of APHIS resources while providing protections to the environment that equal the current prescriptive-based system of regulations.

E. Cumulative Impacts

Cumulative impact is defined by the Council on Environmental Quality's NEPA implementing regulations (40 CFR § 1508.7) as "the impact on the environment which results from the incremental impact of the action when added to other past, present, and reasonably foreseeable future actions regardless of what agency (Federal or non-Federal) or person undertakes such actions. Cumulative impacts can result from individually minor, but collectively significant actions taking place over a period of time." For example, local soil and groundwater impacts could result from the repeated use of a particular field for the production of a GE crop if the crop residues released a substance into the soil that did not readily break down.

This is a programmatic environmental document dealing mainly with broadening the scope of APHIS' regulations and increasing the efficiency and transparency of APHIS' regulatory system for various actions with GE organisms. Cumulative effects in this document will consider the potential environmental impacts of the proposed regulatory changes as well as the past, present, or future actions of other agencies that regulate biotechnology. The focus of the cumulative impact discussion will be those aspects of the environment identified by APHIS in chapter 3, Affected Environment.

The purpose of this analysis is to assess potential effects of making any of the proposed changes in APHIS regulations. Its purpose is not to analyze the cumulative impacts resulting from specific GE organisms. Cumulative impacts analyses related to specific projects, such as permit applications and deregulation decisions, may be prepared at the individual project level, as appropriate, and made available for public comment as part of any NEPA processes necessary for that project. These analyses will be tiered to this EIS and other applicable NEPA documents.

1. The No Action Alternative

APHIS currently regulates the introduction of GE organisms that are plant pests or may be plant pests and also determines when these organisms are no longer regulated by the agency. These functions have been performed for almost 2 decades and, under the No Action alternative, would continue into the future. APHIS has considered whether its program has had cumulative impacts on the environment, that is, impacts caused by the aggregation of past, present, or reasonably foreseeable future actions of this agency or any other entity. The only aspects of APHIS' regulatory program with the potential to aggregate with any past, present, or reasonably foreseeable future actions are the increasing number of GE plants being grown and the increasing number of products on the market

derived from the safe introduction of GE plants. APHIS anticipates that these increases will continue in the future, however, due to the stringency of APHIS' current regulatory program, the agency does not expect any cumulative impacts from the adoption of the No Action alternative.

At the Federal level, the other agencies that were considered with respect to cumulative impacts are EPA and FDA. APHIS has a history of regulating in coordination with these agencies, and takes the regulatory programs of these agencies into account in major regulatory decisions. Since 1986, the Office of Science and Technology Policy (OSTP) has been coordinating the regulation of biotechnology among the agencies. This office ensures that all areas of potential risk are being adequately covered and also tries to minimize overlap where feasible.

Because of the nature of the enabling statutes and the specific areas of responsibility, most GE organisms are regulated by multiple agencies. An organism may be regulated by one, two, or all three agencies. The fact that many products are regulated by multiple agencies does not necessarily imply redundancy. Under the varying authorities, the agencies are generally looking at different types of risks for a given organism. Table 4–3 shows examples of certain plant/trait combinations and indicates which agencies exercise regulatory oversight. Importantly, APHIS has a regulatory role in every example and will be the sole regulator for some organisms. In these cases, it is especially important to have regulations that are sufficiently broad in scope to ensure that GE organisms which could have an adverse impact are regulated and that relevant environmental issues are being addressed.

The cumulative impacts for APHIS' regulatory decisions on individual GE organisms are considered in other NEPA documents prepared on a case-by-case basis as decisions are made. In addition, ongoing coordination with the other Federal agencies through the OSTP process allows individual agencies to adjust policies as needed without affecting other agencies' ability to regulate. Under the Federal system of coordinated regulation, effective regulation at the individual agencies and collaboration, when needed, reduce the likelihood of incremental and cumulative adverse impacts.

2. The Action Alternative (Revise the Regulations)

The discussions that initiated the process of revising the regulations were conducted by OSTP in consultation with the other Federal regulatory agencies. One of the primary goals was to ensure an adequate scope of regulation, recognizing the rapidly evolving technology and the increased interest and research activity in using field crops to produce commercially valuable compounds such as those with pharmaceutical and industrial uses. The group explored available alternatives for addressing the issue

and concluded that it was appropriate and advantageous for APHIS to revise its regulations to fully utilize the PPA of 2000.

There is one clear example of a specific effect that these regulatory revisions might have on other Federal agencies. Since the nature of the new permitting system may provide motivation for developers to go to either EPA or FDA early in the field testing process to address food safety issues, there could be an increase in workload to one or both of those agencies. However, both agencies are fully aware of APHIS' plans and either already have processes in place or are implementing processes to handle such requests. The Action Alternative will offer new levels of protection to human health by encouraging developers to address key issues of food safety early in the development stage and thus, should reduce the risk of adverse impacts.

Table 4–3. Examples of Federal Regulation of Various Types of GE Plants by EPA, FDA, and USDA

New Trait/Organism	Regulatory Oversight by	Regulatory Authority
Insect resistance in a food crop, e.g., Bt corn	APHIS	Safety for agriculture and the environment
	EPA	Safety for the environment, and food/feed safety of pesticidal compound
	FDA	Safety for food and feed use
Modified oil content in a food crop, e.g., oleic acid in soybean seed	APHIS	Safety for agriculture and the environment
	FDA	Safety and labeling for food and feed use
Herbicide tolerance in a food crop, e.g., glyphosate-tolerant corn	APHIS	Safety for agriculture and the environment
	EPA	Safe use of companion herbicide
	FDA	Safety for food and feed use
Insect resistance in a forest non-food tree species	APHIS	Safety for agriculture and the environment
	EPA	Safety for the environment and food/feed safety of the pesticidal compound
Modified flower color in an ornamental crop, e.g., blue carnation	APHIS	Safety for agriculture and the environment

Because the general concepts of the regulatory revision were developed in consultation with the other Federal agencies which regulate GE organisms, it is not anticipated that these revisions would increase the potential for adverse cumulative impacts. In fact, broadening the regulatory scope and strengthening the regulations should provide additional protection to the environment, incrementally and cumulatively. In implementing any new regulations, APHIS will continue to work closely with the other agencies to ensure that revised regulations neither produce unnecessary regulatory duplication nor affect the other agencies' regulatory oversight in some way that would result in adverse cumulative impacts. NEPA documents prepared in conjunction with case-by-case decisionmaking at APHIS will continue to be used to examine cumulative impacts on regulatory decisions for specific GE organisms.

APHIS has long-standing working relationships with State regulatory officials and strives to keep them informed regarding introductions of GE organisms under APHIS' oversight. There have been no cumulative impacts resulting from the aggregation of effects from APHIS' current regulations and State actions. APHIS anticipates that the proposed regulatory revisions will not result in changes to cumulative impacts from any regulation of biotechnology at the State or local levels.

APHIS has determined that each of the proposed actions to be adopted in the preferred alternative is either as environmentally protective or more protective than the provisions in the current regulations. Should APHIS adopt the preferred alternative, no past, present, or reasonably foreseeable actions by APHIS or other agencies will change the magnitude of the cumulative impacts resulting from our regulatory program. APHIS has therefore determined that there will be no new significant cumulative impacts as a result of the proposed regulatory changes.

F. Other Considerations

APHIS is also using this rule-revision process to implement several administrative changes to its rules. Unlike revisions discussed elsewhere in this DEIS, these changes are intended to improve the clarity, coordination, and execution of the rules themselves. Proposed changes include the following:

1. Administrative Changes to APHIS Rules

- Additional information requirements for applicants.
- Clarification of the relationships between various sections of the rule.
- Inclusion of provisions for electronic permit applications.
- Modification of time limits for agency response to applicants.
- Requirements for additional data reports for field tests.

- Clarification of permit expiration dates.
- Clarification of permit renewal processes.

There is no evidence that any of these administrative changes could have significant environmental impacts.

2. Impacts on Threatened and Endangered Species

Threatened and Endangered Species (TES) are plants and animals at risk of becoming extinct throughout all or part of their geographic range. Species can be designated (listed) under the Federal Endangered Species Act of 1973, listed under parallel State laws, or both.

APHIS' BRS program has no known direct adverse effects on threatened or endangered plants or animals, on species proposed for listing, or on designated critical habitats. Similarly, BRS program activities thus far have not directly protected or benefited listed TES, species proposed for listing, or designated critical habitats. However, there may be indirect beneficial or adverse effects. For example, as discussed in chapter 3, the deregulation of plants resistant to insects via Bt toxin production has resulted in a reduction in the use of chemical insecticides, which indirectly reduces adverse impacts on many nontarget organisms, some of which could be TES. On the other hand, if a threatened or endangered insect species feeds on a Bt crop, that insect species may be adversely affected. Herbicide-tolerant plants may also have indirect beneficial or adverse effects on TES via changes in herbicide use and changes in cultivation frequency or other agronomic practices.

Theoretically, other GE traits could result in indirect beneficial or adverse effects. For example, traits improving crop nutritional quality could benefit TES feeding on those crops. Alternatively, if a crop plant is given a gene which creates a plant sufficiently competitive to become invasive in natural habitats, threatened and endangered plant species could be displaced or threatened and endangered animal species may lose a preferred food plant or be otherwise affected by the alteration of their habitat.

Indirect impacts are difficult to quantify or even detect in many cases, especially when the analysis is at the programmatic level. Although APHIS acknowledges the possibility of programmatic impacts on TES, on species proposed for listing, or on designated critical habitat, APHIS' approach is to analyze these impacts at the project level, as described below, in order to avoid or minimize any impacts. The analysis depends on the regulated activity under consideration:

- Under normal circumstances, the interstate movement and importation of regulated articles should have no effect on TES, species proposed for listing, or designated critical habitat because persons shipping regulated articles are required to use packaging that prevents environmental releases. In APHIS' experience, package requirements have been extremely effective in preventing accidental environmental releases. However, should an accident occur that causes a package to fail to completely contain the regulated article, APHIS anticipates any release from the package will be localized and readily cleaned up, resulting in no significant impacts on TES, species proposed for listing, or designated critical habitat.

- Impacts to TES, proposed species for listing, or designated critical habitat due to field tests of regulated articles are currently and would continue to be evaluated for every permit application that involves a field trial, taking into account the size of the trial, the plant species, the GE trait involved, APHIS familiarity with the plant/trait combination, and the geographic location. APHIS currently uses a TES decision worksheet which asks a series of questions regarding proposed field trials. Answers to these questions enable APHIS to determine the likelihood that a proposed field trial will affect TES, proposed species for listing, or designated critical habitat and whether consultation with the FWS is appropriate. In special cases, such as plants producing pharmaceutical or industrial compounds, APHIS may also consult with other agencies, such as FDA and EPA, regarding effects on endangered species.

- Petitions for deregulation or approval may result in an APHIS determination that the plant in question may be planted without any restrictions, essentially anywhere in the United States. APHIS, therefore, must determine which, if any, TES or species proposed for listing will come into contact with the deregulated plant, and whether that contact will affect those species or any designated critical habitat. APHIS will consult with the FWS if species or habitats are identified that may be affected. In the special case involving Bt crops, EPA performs an analysis in addition to the one prepared by APHIS, and EPA may restrict the planting of the crop in areas where an endangered insect, such as a butterfly, may feed on the crop and suffer adverse effects.

Appendix A. Acronyms and Glossary

A

Abiotic Stress — Stress due to non-living, environmental factors such as cold, heat, drought, flooding, salinity, toxic substances, and ultraviolet light.

Agrobacterium tumefaciens — A bacterium that causes crown gall disease in some plants. The bacterium characteristically infects a wound and incorporates a piece of its own DNA into the host plant genome, causing the host cell to grow into a tumor-like structure. This DNA-transfer mechanism is commonly exploited in the genetic engineering of plants.

***Agrobacterium tumefaciens*-mediated Transformation** — The process of DNA transfer from *Agrobacterium tumefaciens* to plants, which occurs naturally during crown gall disease and can be used as a method of transformation.

Allele — One of several alternate forms of a gene occupying the same location on the chromosome.

Allelochemical — A chemical produced by a plant of one species that has a detrimental effect on plants of other species.

Antibiotic Resistance Marker Gene — Genes (usually of bacterial origin) used as selection markers in transformation because their presence allows cell survival in the presence of normally toxic antibiotic agents.

Antisense DNA — The DNA strand complementary (hence "anti") to the mRNA, i.e., the non-transcribed strand.

Antisense Gene — A gene that produces an mRNA complementary to the transcript of a normal gene. (See Antisense RNA.)

Antisense RNA — An RNA sequence that is complementary to, and binds, with all or part of a functional mRNA molecule, thereby, blocking its translation.

AOSCA — American Organization of Seed Certifying Agencies.

APHIS — Animal and Plant Health Inspection Service.

Arabidopsis thaliana — A small plant in the mustard (Brassicaceae) family, also known as thale cress. *Arabidopsis* is commonly used as a model for studying plant genetics.

B

Backcrossing — Crossing an individual with another organism that is genetically identical to its parent. The offspring of such a cross are referred to as the backcross generation or backcross progeny.

***Bacillus thuringiensis* (Bt)** — A common soil bacterium, notable for its ability to produce proteins which are toxic to certain categories of insects. (See Cry proteins.)

Bioaccumulation — The increase in the concentration of a chemical in biological systems over time as compared to the chemical's concentration in the environment.

Biological Control Agent, Biocontrol Agent — Any enemy, antagonist, or competitor used to control a plant pest or noxious weed. (See Plant Protection Act of 2000, 7 U.S.C. 7702.)

Biolistics — A technique to generate genetically engineered cells, in which DNA-coated microscopic metal particles, usually tungsten or gold, are propelled by various means ("gene guns") fast enough to puncture target cells. Provided that the cell is not killed, the DNA may be taken up by the cell and incorporated into the cell's genome. (Synonym: microprojectile bombardment.)

Biomagnification — The process that results in the accumulation of a chemical in an organism at higher levels than are found in its food; occurring when a chemical becomes more and more concentrated as it moves up the food chain.

Biotechnology — Making specific modifications to the genome of an organism using techniques based on molecular biology, such as genetic engineering, gene transfer, DNA typing, and cloning of plants and animals.

BLASTP — BLASTP (Altschul, 1990) is a computer program that searches for similarities between the amino acid sequence of a protein and other amino acid sequences.

BNF — Biotechnology Notification File.

BRAD — Biopesticides Registration Action Document.

Breeding — The process of sexual reproduction and production of offspring. Plant breeding is an applied science for the development of plants suited for the use of humans, rather than their ability to survive in the wild.

Breeder Seed Seeds of a particular plant variety maintained by a plant breeder, usually at a very high level of purity, that serves as the source for all subsequent generations of seed production. (See Foundation Seed.)

BRS Biotechnology Regulatory Services (USDA–APHIS).

Bt *Bacillus thuringiensis.*

Bt Proteins, Bt Toxins See Cry proteins.

C

CBI Confidential business information.

CEQ Council on Environmental Quality.

Certified Seed Seed produced to specific standards to assure purity and freedom from weed seeds and seedborne pathogens, which is used for commercial production of the crop.

CFR Code of Federal Regulations (U.S.).

Codex Alimentarius Commission An international food safety standard setting body (part of the Food and Agriculture Organization and the World Health Organization of the United Nations) responsible for developing international food standards.

Coding Sequence That portion of a gene which directly specifies the amino acid sequence of its product. Non-coding sequences of genes include introns and control regions such as promoters, operators, and terminators.

Confined Describes a field test or other environmental release of a transgenic organism performed under terms and conditions intended to minimize establishment and spread into, and interaction with the environment of the transgenic organism and any progeny derived from it.

Competent Bacteria Bacteria able to take up and stably incorporate foreign DNA.

Conservation Tillage A broad range of soil tillage systems that leave crop residue on the soil surface, substantially reducing the effects of soil erosion from wind and water.

Constitutive Expression Describing a gene that is expressed (i.e., "turned on") at a relatively constant level in all cells of an organism without regard to cell environmental conditions.

Construct An engineered piece of DNA designed to be transferred into a cell or tissue. Typically, the construct comprises a gene or genes of interest, a marker gene, and appropriate control sequences, often from different organisms, as a single package. A repeatedly used construct may be called a "cassette."

CPB Cartagena Protocol on Biosafety

Cross Protection Complete or partial resistance to a plant virus that is generated by the introduction of a similar, usually less virulent, plant virus.

Cry Proteins A class of crystalline proteins produced by strains of the soil bacterium, *Bacillus thuringiensis*. These proteins are toxic to certain categories of insects (e.g. corn borers, corn rootworms, mosquitoes, black flies, armyworms, tobacco hornworms, some types of beetles, etc.), but are harmless to mammals and most beneficial insects. Synonyms: delta endotoxins, *Bt* toxins.

D

Deoxyribonucleic Acid (DNA) A nucleic acid that carries the genetic information of a cell. The structure of DNA is two long chains, consisting of chemical building blocks called 'nucleotides,' twisted into a double helix. The order of nucleotides determines hereditary characteristics.

Dicot A flowering plant with two embryonic seed leaves. Examples include oaks, maples, roses, beans, mustards, and cacti. (See Monocot.)

Disease Resistance The genetically determined ability to prevent the invasion or reproduction of a pathogen, thereby allowing the resistant individual to remain healthy. Disease resistance may operate by pathogen exclusion, by preventing pathogen spread, or by tolerating pathogen-produced toxins.

DNA See Deoxyribonucleic Acid.

Deoxyribonucleic Acid A nucleic acid that carries the genetic information of a cell. The structure of DNA is two long chains, consisting of chemical building blocks called 'nucleotides,' twisted into a double helix. The order of nucleotides determines hereditary characteristics.

Donor An organism that provides a gene or gene fragment used in the genetic transformation of another organism, called the "recipient."

E

ELISA (enzyme-linked immunosorbent assay) A sensitive assay for detecting a specific protein that uses antibodies to bind to the protein.

Encapsidation The process by which the genetic material of a virus is enclosed in a protein coat (the capsid).

Endospermatic Seed Seed having an endosperm, the nutritive tissue surrounding the seed embryo.

EPA U.S. Environmental Protection Agency.

Epistatic Effects The result of one gene suppressing the effect of a different gene.

EUP Experimental Use Permit.

Event See Transformation Event.

Expression The means by which a gene's information stored in DNA (or RNA in some viruses) is turned into biochemical information such as RNA or protein.

F

FASTA FASTA (Pearson, 1988) is a computer program that searches for similarities between one nucleic acid sequence and other sequences.

FDA Food and Drug Administration.

Fecundity The capacity for producing offspring. In a scientific context, this usually refers to the number of offspring (i.e. seeds).

FFDCA Federal Food, Drug, and Cosmetic Act.

FIFRA Federal Insecticide, Fungicide and Rodenticide Act.

Flanking Region The DNA sequences extending on either side of a specific sequence.

Foundation Seed Seed of a particular plant variety that is produced from breeder seed and is then planted to produce certified seed used for commercial production. (See Breeder Seed and Certified Seed.)

FPPA Federal Plant Pest Act.

G

GE See Genetically Engineered.

Gene The basic unit of heredity transmitted from generation to generation during sexual or asexual reproduction; an ordered sequence of nucleotide bases comprising a segment of DNA. A gene contains the sequence of DNA that encodes an individual RNA or protein.

Gene Expression The process by which a gene produces mRNA and protein and ultimately exerts its effect on the phenotype of an organism.

Gene Flow The spread of genes from one population to another by the movement of individuals, pollen, seeds, or spores.

Gene Insertion The incorporation of one or more copies of a gene into a chromosome.

Gene Product A RNA or a protein (e.g. an enzyme), the production of which is directed by the corresponding gene.

Gene Silencing Loss of gene expression either through an alteration in the DNA sequence of a structural gene or its regulatory region or through interactions between its transcript and other mRNAs present in the cell. (See Antisense RNA.)

Gene Splicing The enzymatic attachment of one gene or gene fragment to another.

Genetic Engineering Genetic engineering refers to the process in which one or more genes and other genetic elements from one or more organism(s) are inserted into the genetic material of a second organism using recombinant DNA techniques.

Genetically Engineered (GE) Modified in genotype and, hence, phenotype using recombinant DNA techniques.

GE Organism Genetically engineered organisms. (See Genetically Engineered.)

GE Plant Genetically engineered plant. (See Genetically Engineered.)

Gene Stacking The use of plant breeding to combine two or more genetically engineered traits into a single plant variety.

Genetic Marker A gene that is a reliable indicator that a particular organism possesses a specific trait of interest. Markers may be used to select certain individual organisms, e.g., cells that have inherited resistance to an antibiotic will be the only ones in a population that survive an antibiotic treatment.

Genetic Transformation See Transformation.

Genome All of the hereditary material in a cell including DNA present in the cell nucleus, as well as in other locations such as plant chloroplasts and mitochondria.

Genomics The study of the entire genome of an organism, often in comparison to the entire genome of another organism (i.e. comparative genomics).

Genotype The total genetic makeup that an individual receives from its parents.

GRAS Generally recognized as safe.

GUS Beta-glucuronidase; a reporter of gene system used to analyze the activity of promoters (in terms of expression of genes under those promoters) either quantitatively or qualitatively through visualization of its activity in different tissues.

H

Halophyte A plant adapted to living in very salty (saline) soils.

Herbicide Resistance or Tolerance The ability of a plant to remain relatively unaffected by the application of what would otherwise be a highly damaging dose of an herbicide.

Heterologous Encapsidation The phenomenon where the coat protein of one virus is able to encapsidate the nucleic acid of a different virus. (See Encapsidation.)

HGT Horizontal gene transfer

High Dose Twenty-five times the dose necessary to kill all susceptible insects.

Homologous Recombination The physical exchange of genetic material between two closely related or similar genetic sequences.

Horizontal Gene Transfer — The transfer of genetic material from one organism (the donor) to another organism (the recipient) that is not sexually compatible with the donor.

Human Environment — According to the Council on Environmental Quality, the term *human environment* "shall be interpreted comprehensively to include the natural and physical environment and the relationship of people with that environment." 40 CFR § 1508.14

Hybrid — The offspring of two genetically dissimilar organisms.

I

Industrial Plant — A plant genetically engineered with a gene whose effect is primarily of industrial use, as opposed to an agricultural or nutritional purpose.

Inserted Gene — A piece of DNA that has been inserted into an organism using recombinant DNA technology.

Instar — A stage in the development of an insect between two successive molts.

Interfertile — Two plants or groups of plants capable of interbreeding and producing offspring.

Introgression — The introduction of genes from one species into the gene pool of another via sexual crossing. The process begins with hybridization between the two species, followed by repeated backcrossing to one of the parent species.

IPM — Integrated pest management.

IRM — Insect resistance management.

L

LD — See Lethal Dose.

LD_{50} — Median lethal dose or dose needed to kill 50 percent of a population of test organisms.

$LD_{99.9}$ — The dose that kills 99.9 percent of a population of test organisms.

Lethal Dose (LD) — The amount of a test substance that will kill one or more individuals in a test population.

LMO — Living genetically modified organisms

LMOFFP Living genetically modified organisms imported only for food, feed, or for processing

M

Marker Gene A gene of known function or known location that is inherited in Mendelian fashion and facilitates the study of inheritance of a nearby gene.

Marker-assisted Selection The use of DNA markers to select the organisms that possess genes for a particular phenotype desired for subsequent breeding/propagation. This allows selection without having to screen for the performance trait itself, which may be difficult.

Monocot A flowering plant with only one embryonic seed leaf. Examples include grasses, irises, lilies, and onions. (See Dicot.)

MOU Memorandum of Understanding.

Mutagen A chemical or dose of radioactivity capable of producing a genetic mutation by causing changes in the DNA of living organisms.

Mutagenesis Induction of heritable change(s) in the genetic constitution of a cell through alterations to its DNA, most often via treatments with chemicals or ionizing radiation.

N

NASDA National Association of State Departments of Agriculture.

NCIE National Center for Imports and Exports.

NEPA The National Environmental Policy Act of 1969 and subsequent amentments.

NOI Notice of Intent.

Non-propagative See Non-viable Plant Material.

Non-viable Plant Material Broadly speaking, all plant tissues other than viable propagules, such as seeds, bulbs, tubers, etc. That is, all tissues dead or alive which cannot directly result in the propagation of a new plant.

Noxious Weed Any plant or plant product that can directly or indirectly injure or cause damage to crops (including nursery stock or plant products), livestock, poultry, or other interests of agriculture, irrigation, navigation, the natural resources of the United States, the public health, or the environment. (Plant Protection Act of 2000, 7 U.S.C. 7701 et seq.)

NRC National Research Council.

O

Obligate Parasite A parasite that cannot live independently of its host.

OECD Organisation for Economic Co-operation and Development.

Open Reading Frame (ORF) A sequence of nucleotides in a DNA molecule that has the potential to encode a peptide or protein. The term is generally applied to sequences of DNA for which no function has yet been determined. The number of ORFs provides an estimate of the number of genes transcribed from the DNA sequence.

ORF See Open Reading Frame.

Osmoprotectant Compounds accumulated by plants during drought conditions to reduce water stress.

OSTP Office of Science and Technology Policy.

Outcrossing The tendency of a plant species to produce offspring that result from the mating of two different individual plants. (See Self-pollinated.)

P

Pathogen-derived Resistance Resistance to a disease conferred by something derived from the disease-causing agent itself. Example: coat protein mediated viral resistance.

Performance-based Standards A form of regulation in which required *outcomes* are defined by regulation, but the actions or conditions necessary to attain the outcomes are not defined by regulation. Contrast with a *prescriptive* standard, which specifies actions or conditions that must be followed to attain the required outcome.

Phenotype The appearance or other characteristics of an organism, resulting from the interaction of its genetic constitution with the environment.

Phytoremediation	The use of plants to remove or reduce pollutants in soil by production of compounds that stimulate their degradation or by uptake of pollutants through roots and accumulation in plant tissues.
PIP	See Plant Incorporated Protectant.
Plant Incorporated Protectants (PIPs)	Plant-Incorporated Protectants (PIPs) are pesticidal substances produced by plants and the genetic material necessary for the plant to produce the substance. (http://www.epa.gov/pesticides/biopesticides/pips/current_pip_eups.htm)
Plant Pest	Any living stage (including active and dormant forms) of 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 agents or substances, which can directly or indirectly injure or cause disease or damage in or to any plants or parts thereof, or any processed, manufactured, or other products of plants. (7 CFR 340.1)
Pleiotropic Effects	A phenomenon in which a single genetic alteration affects multiple phenotypic characteristics, such as a single gene affecting flowering, leaf shape, and growth rate.
PMP	Plant manufactured pharmaceutical.
Post-translational Modification	The addition of specific chemical residues to a protein after it has been translated. Common residues are phosphate groups (phosphorylation) and sugars (glycosylation).
PPA	Plant Protection Act.
PPQ	Plant Protection and Quarantine (USDA, APHIS).
PQA	Plant Quarantine Act.
Primer	A short, single-stranded piece of DNA or RNA that, when annealed to a long template of single-stranded DNA, provides a doubled-stranded structure from which DNA polymerase will synthesize a new DNA strand to produce a duplex molecule.
Proline	An amino acid. Some plant cells accumulate proline as an osmoprotectant.

Promoter A region of DNA located upstream of a gene that controls to what degree, where, and/or when a gene is expressed.

Propagules Any part of a plant that can be detached from the organism and propagated in order for it to grow into a new plant.

Proteomics A research approach that seeks to identify and characterize proteins and protein–protein interactions in a given species.

Protoxin A precursor of a toxin that requires additional modification before acquiring its toxic properties.

Pyramid In the context of PIPs, the presence of multiple resistance genes that target the same pests with possible overlap in the mode of action. For example, a corn or cotton plant containing a Cry1A protein and a Cry2A protein active against the same lepidopteran pest such as the European corn borer or tobacco budworm is termed a "pyramid."

R

Recombinant DNA Technology The manipulation of DNA in which DNA, including DNA from different organisms, is cut apart and recombined using enzymes.

Recombination The physical exchange of genetic material between two genetic sequences that produces new combinations of genetic information. (See Homologous recombination and Non-homologous recombination.)

Refuge Part of a habitat where an individual can avoid a mortality agent. In the context of Bt crops a refuge consists of non-Bt host plants that are managed to provide sufficient susceptible adult insects to mate with potentially Bt-resistant adult insects to decrease the number of resistant insects and dilute the frequency of resistance genes.

Regulated Article Subject to APHIS regulation under 7 CFR part 340.

Rhizosphere The root surface together with that region of the surrounding soil in which the microbial population is affected by the presence of the root and root exudates.

Ribonucleic Acid (RNA) A nucleic acid composed of a long, often single-stranded chain of chemical building blocks called 'nucleotides.' RNA has multiple functions in the process of translating information stored in genes (DNA) into proteins.

Risk Analysis A process consisting of three components—risk assessment, risk management, and risk communication—that is performed to understand the nature of unwanted, negative consequences to human and animal health or the environment.

Risk Assessment A scientifically based process consisting of the following steps: (i) hazard identification; (ii) hazard characterization; (iii) exposure assessment; and (iv) risk characterization.

Risk Communication The interactive exchange of information and opinions throughout the risk analysis process concerning hazards and risks, risk-related factors, and risk perceptions, including the explanation of risk assessment findings and the basis of risk management decisions.

Risk Management The process, distinct from risk assessment, of weighing policy alternatives, in consultation with all interested parties, considering risk assessment and other factors relevant for the protection of consumer health and for the promotion of fair trade practices, and, if needed, selecting appropriate prevention and control options.

RNA See Ribonucleic Acid.

Rotation

- In forestry, the number of years required to establish and grow trees to a specified size, product, or condition of maturity. A pine rotation may range from as short as 20 years for pulpwood to more than 60 years for sawtimber. Full rotation is the total time from planting to harvest. Half rotation would be approximately half the time to reach maturity or harvest.
- In crop production, the cycle of crops grown in successive years in the same field. Rotations are instituted to limit the spread and accumulation of diseases (especially soil-borne diseases) and pests and to manage plant nutrients.

S

Secondary Metabolism The production by living organisms of substances not essential for primary metabolic functions or physiology. Their role is associated with interaction with the environment, for example as defense or as attractants. Some of these have useful pharmacological or nutritional properties, while others are toxic.

Self-pollinated The tendency of a plant species to produce offspring that result from a flower pollinating itself. (See Outcrossing.)

Stratification Chilling or warming seeds, for a period of time, to improve germination.

Stress Tolerance Gene A gene which confers upon a plant an increased ability to withstand an environmental stress, such as drought, temperature extremes, or soil salinity.

Synergy The interaction of two or more factors so that their combined effect is greater than the sum of their individual effects.

T

TES Threatened and Endangered Species.

Trait A characteristic of an organism that manifests itself in the phenotype. Traits may be the result of a single gene or may be polygenic, resulting from the simultaneous expression of more than one gene.

Transcription The process by which a messenger RNA (mRNA) is created from the nucleotide sequence of a gene (DNA).

Transencapsi-dation See Heterologous encapsidation.

Transformant A cell or organism that has been genetically altered through the integration of a transgene(s). A "primary" transformant is the first generation following the transformation event.

Transformation The uptake and integration of DNA in a cell's genome, in which the introduced DNA is intended to change the phenotype of the recipient organism in a predictable manner.

Transformation Event A single successful integration of a gene or gene fragment into a cell or a successful deletion of a gene or gene fragment from a cell.

Transgene A foreign gene that is inserted into the genome of a cell via recombinant DNA techniques.

Transgenic Organism An organism whose genome has been modified via the stable incorporation of a piece of foreign DNA (a transgene).

Translation The process by which the sequence of nucleotides in a messenger RNA (mRNA) directs the sequence of amino acids in a new protein during protein synthesis.

Trophic Relating to the feeding habits or food chain of different organisms in a food chain.

TSCA Toxic Substances Control Act.

V

VCP See Viral Coat Protein.

Vector The agent, such as a plasmid, used by researchers to carry new genes into cells.

Viral Coat Protein A protein produced by a virus that forms a protective layer, or *capsid*, around the genetic material of the virus.

Volunteer Plants resulting from crop seed that escapes harvest and remains in the field until subsequent seasons, where it germinates along with the succeeding crop.

W

Weediness The ability of a plant to colonize a disturbed habitat and compete with cultivated species.

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Appendix C. Public Scoping Comments

Members of the public were invited to participate in the scoping process for this DEIS through an announcement of a notice of intent (NOI) to prepare an environmental impact statement (EIS) on options under consideration to change 7 CFR 340 in the Federal Register (FR) (Docket Number 03–031–2, 69 FR 3271–3272). In this NOI, APHIS asked for comment on 11 issues. The public responded to these 11 issues and provided other information outside of the scope of these issues. The comment period opened on January 23, 2004. During this comment period, which closed on April 13, 2004, APHIS received 3,996 comments. Comments were made by public interest groups, industry representatives, industry trade organizations, private individuals, State and Federal agency representatives, agricultural producers (including growers and food processors), and marketing groups.

Full text of the comments received during the open comment period is available online at: http://www.aphis.usda.gov/brs/eis/eis_comments.html

Many of the comments were submitted as form letters. The issues raised by the form letter submissions include:

- GE corn, *Bt* crops, and pharmaceutical and industrial crops should not be allowed to be grown outdoors.
- New regulations must include a comprehensive assessment of the economic impacts genetically engineered (GE) crops have had on family farmers and rural communities, and a socioeconomic assessment for all new GE crop and food varieties.
- There should be no exemptions for the occurrence of low levels unapproved GE varieties in the food supply.
- Plant and animal species used for food or feed should not be used to produce pharmaceuticals or industrial chemicals.

Several comments address issues related to maintaining biological or physical confinement of GE varieties from non-genetically engineered varieties. These include several comments that relate to:

- Concern for pollination of non-GE crops by GE crops.
- Concern for food choice for consumers who do not wish to purchase GE food.
- Maintenance of non-GE seed stocks.
- Segregation of plants that are engineered to produce pharmaceutical and industrial compounds from the food and feed supply.
- Implications for international trade.
- Implications for biodiversity abroad.

Several comments suggest possible rule changes or agency practices:

- Elimination of petitions for non-regulated status.
- Establishment of a two-tiered permitting process, with experimental permits for field trials and commercial permits for GE crops that are to be sold in commerce.
- Publication of applications for notifications, permits, and petitions upon receipt, before environmental analysis or risk assessment.
- Soliciting public comment before any permit can be granted.

Some comments focused on the eventual development of resistance of natural populations to the intended actions of the genetically incorporated molecules. There is a concern that tools will be lost to growers or land managers as the targeted populations develop resistance to these tools. In addition, APHIS also received many comments that directly address the 11 issues that were presented in the NOI. These comments are summarized by issue below.

Question 1—APHIS is considering broadening its regulatory scope beyond GE organisms that may pose a plant pest risk to include GE plants that may pose a noxious weed risk and GE organisms that may be used as biological control agents. Do regulatory requirements for these organisms need to be established? What environmental considerations should influence this change in regulatory scope?

The majority of comments agreed that APHIS should broaden its regulatory scope to include GE organisms that may pose a noxious weed risk or that may be used as a biological control agent. Some comments raised environmental risk concerns as a reason to broaden APHIS' authority. Others cite a belief that GE plants are inherently a greater environmental risk than conventionally bred plants.

Some respondents disagree because they believe that APHIS' current practice of evaluating plant pest risk is more than adequate to protect American agriculture. Many of these comments cite the belief that these plants are not inherently different from conventionally bred plants.
A few comments suggest that it is important that APHIS coordinate any changes to its practices with the other agencies in the coordinated framework.

Question 2—APHIS is considering revisions to the regulations that would define specific risk-based categories for field testing, including (a) product types shown to pose low pest and environmental risks; (b) product types considered to pose a noxious weed risk, of unknown plant pest or noxious weed risk, containing sequences of unknown phenotypic function, and involving new plant-incorporated protectants that have not completed applicable review at EPA; and (c) pharmaceutical or industrial crops not intended for food or feed. What environmental factors should be considered in further delineating such requirements? What criteria should be used to establish the risk-based categories? Should certain low-risk categories be considered for exemption from permitting requirements? If so, what criteria should apply?

Several comments support the use of specific risk-based categories for field testing. Several factors were presented for considering risk groups. These include the origins of the trait (e.g. is the gene from the same species or a closely related species), the type of trait expressed (e.g. plant incorporated protectants), the ability of the plant to reproduce sexually (e.g. male sterile, complete sterility, degree of selfing), potential environmental impacts, the end use of the product (e.g. plants engineered to produce pharmaceuticals or industrials), size of the field trial, or APHIS' familiarity with the trait-crop combination.

Other comments did not support the use of specific risk-based categories. These comments support the use of case-by-case evaluations of each new GE plant.

Question 3—APHIS is considering ways to provide regulatory flexibility for future decisions by allowing for commercialization of certain GE organisms while continuing, in some cases, to regulate the organisms based on minor unresolved risks. Other regulated articles could be treated as they have been under the current system, in which all regulatory restrictions are removed. What environmental factors should be considered in distinguishing between these kinds of decisions?

Most comments do not support this type of regulatory flexibility without clearly defining the methods, mechanisms, and criteria by which products will be evaluated. Legal, environmental and economic risks are cited as reasons for apprehension in adopting this type of regulatory vehicle. Comments include conditional support for commercialization of regulated articles if, for example, commercial approval could not be revoked. Others believe that commercialization of regulated articles could be prudent if data is collected on large-scale environmental impacts and the product could be withdrawn from the market if significant environmental impacts were documented. One comment suggests that APHIS already has the authority to allow commercialization of regulated articles under its current regulations.

Some comments support the proposal but again suggest that "minor unresolved risks" be defined. Some of these comments support the use of tiered systems for the commercialization of crops, and crops that have low risk could be commercialized while data is collected. For other cases, for example, plants that produce pharmaceutical compounds, one comment suggested that a gradual reduction in restrictions could be mandated as more information and familiarity are gained with a particular crop.

Question 4—Are there changes that should be considered relative to environmental review of, and permit conditions for, GE plants that produce pharmaceutical and industrial compounds? Should the review process, permit conditions, and other requirements for non-food crops used for production of pharmaceutical and industrial compounds differ from those for food crops? How should results of a food safety evaluation affect the review, permit conditions, and other requirements for these types of plants? How should the lack of a completed food safety review affect the requirements for these types of plants?

Several comments demonstrate concern for the use of food or feed crops to produce pharmaceutical and industrial crops. Some comments suggest that these crops can be used with

strict confinement conditions. Other comments suggest that the current system, or one that is more relaxed, would be preferred. Many comments suggested that FDA protein safety review should be sought before permits for field trials can be granted. The issues raised include:

- These products should remain regulated after they are commercialized.
- They should be grown under strict isolation so they cannot contaminate the food and feed channels.
- They should be considered high risk due to the hazards of the GE traits entering wild relatives or food, forage, or fiber crops through cross-pollination.
- Food or feed crops should not be used to produce plant-manufactured pharmaceuticals (PMPs) or plant-manufactured industrial compounds (PMICs) commercially without effective controls, multiple containment measures, and procedures to ensure no contamination of the food supply occurs.
- All industrial feedstock and PMP/PMIC crops are not necessarily a separate class of crops that require regulation, particularly where a similar phenotype could be obtained via conventional means.
- Simply because these proteins are in the environment does not necessarily make them environmental contaminants or human health hazards. Regulations should be highly differentiated for different classes of PMP/PMIC crops based on the level of risk from inadvertent consumption/contact by humans and animals. If warranted, due to the toxicological properties of the product in question, USDA should coordinate with EPA and FDA to establish acceptable, legal levels of adventitious presence for different classes of compounds based on such early assessments, which can be revised as toxicological data grow.
- Additional allowances towards relaxed regulation of PMP/PMIC crops should be made when:
    - The plant is not a food or feed crop, nor capable of crossing with a food or feed crop, or only inert materials are used as minor components in food (e.g., non-nutritive fiber).
    - The crop is grown far outside of its normal area of production.
    - The crop outcrosses at a very low level (e.g., usually below 1 percent in small grain cereals).
    - The transgene is in the chloroplast genome or the GE plant is a female in a dioecious species.
    - The seed parent of a hybrid crop is male-sterile and the pollen donor is not transgenic.
    - Genetic markers are used to easily distinguish the PMP/PMIC crops from their commercial counterparts (e.g., purple corn, black soybean, modified leaves in vegetative crops, etc.), such that mixtures could be readily detected.
    - Crops are engineered to have complete (male and female) sexual sterility and can be vegetatively propagated.
- Regulatory approval should not be granted to any GE organism without an appropriate food safety review.
- The Iowa Protocol for Risk Assessment of Genetically Enhanced Crops was suggested as a basis for developing a factual and consistent methodology on an application-to-application

basis for developing risk tolerances. Based on the risk factor, appropriate growing conditions within a permit can be established.

- Specific risk categories are worth considering for PMP/PMIC GE crops:
    - Whether the host plant is a food crop or a non-food crop.
    - The potential toxicity of the engineered compound.
- It is the responsibility of FDA to determine whether GE crops pose any food-safety risks. Although the noxious weed provisions of the Plant Protection Act may allow USDA to assess and address how noxious weeds might affect humans, those provisions should not be interpreted so broadly as to provide APHIS with the legal responsibility or authority to determine the food safety of GE crops or to prevent engineered crops from entering the food supply.
    - The current permit conditions for PMP and PMIC crops are adequate to protect the environment considering the current scale of production.
    - The agency should work with FDA through the Coordinated Framework to establish a mechanism for food safety evaluations that would be appropriate for these products.

Question 5—"Noxious weed," as defined in the Plant Protection Act, includes not only plants, but also plant products. Based on that authority, APHIS is considering the regulation of nonviable plant material. Is the regulation of nonviable material appropriate and, if so, in what cases should APHIS regulate?

The majority of comments do not support the regulation of nonviable plant material by APHIS. Most respondents agree that FDA or EPA would already have regulatory authority over the nonviable material. However, some comments support the extension of APHIS' regulatory authority to nonviable plant material in specific cases. Some comments express the opinion that if the nonviable material could pose a plant pest risk or a risk to the food supply then it should be regulated. A few comments suggested that nonviable GE plant materials should be regulated to segregate them from non-GE crops and products.

Question 6—APHIS is considering establishing a new mechanism involving APHIS, the States, and the producer for commercial production of plants not intended for food or feed in cases where the producer would prefer to develop and extract pharmaceutical and industrial compounds under confinement conditions with governmental oversight, rather than use the approval process for unconfined releases. What should be the characteristics of this mechanism? To what extent should this mechanism be employed for commercial production of plants not intended for food or feed? What environmental considerations should influence the development of this mechanism?

Some of the issues raised include:

- Confinement measures must address pollen movement and microorganism dispersal.
- Confinement measures should ensure that the food and feed supply are not affected.
- APHIS should consult with other USDA departments (e.g., Federal Crop Insurance Corporation and the Commodity Credit Corporation) to explore the issues of food chain

liability and means for companies developing products to assume appropriate liability for their actions.

- APHIS should consider limiting the production of plant-made pharmaceuticals to nonfood or nonfeed crops.
- GE material must be rendered 100 percent nonviable before leaving the facility in any form.
- Where PMP/PMIC crops are producing high-risk compounds, such that minimal tolerances cannot be established, APHIS might consider limiting their deployment to enclosed conditions, at least until data to the contrary can be provided.
- Closed systems should be used with appropriate checks and traceability reflective of a certified seed and identity preserved program with a monitoring system incorporated.
- A starting point for the types of regulations required might be NIH's guidelines for managing experimental GE plants in greenhouses
- The product development process for pharmaceuticals and industrials should be a stepwise, laddered approach in which all products would initially start out under high restrictions and move, as the data supports, to less restrictive conditions

Question 7—The current regulations have no provision for adventitious presence (AP)—intermittent and low-level presence in commercial crops, food, feed, or seed of GE plant material that has not completed the required regulatory processes. Should APHIS establish a separate component within a revised regulatory system to address adventitious presence? Should the low level occurrence be exempt from APHIS regulation? If so, what are the conditions under which the low level occurrence should be allowed? What environmental considerations would apply to establishment of such allowances?

Most respondents support the establishment of regulatory guidelines for AP of regulated materials in non-regulated materials. Many of the responses support APHIS regulating AP. A few comments question APHIS' authority, and suggest that other agencies or groups would be better equipped to set the levels. One comment suggests that setting levels is difficult if there are no inexpensive methods available to test for the regulated articles. Most respondents agree that the level of AP should be related to the risk presented by the regulated article. Several comments suggest that practices should still be used to attempt to prevent AP from occurring, even if regulations allow for low levels of AP.

Question 8—Should APHIS provide for expedited review or exemption from review of certain low-risk GE commodities intended for importation that have received all necessary regulatory approvals in their country of origin and are not intended for propagation in the United States? What environmental considerations should be applied to determination of any such allowances?

Some comments support the proposal, others support the proposal in part, and some do not support the proposal at all. Some of the issues presented include:

- Potential for escape, or unauthorized planting.
- Differences in regulations between countries.

- Differences in wild relatives in the exporting country.
- Differences in potential environmental effects.
- Opportunity for the United States to set precedent for other countries.
- Comments that support expedited review suggest that the evaluation of the commodity focus on the environmental issues that were not covered in the original country's assessment.
- The Biosafety Clearing-House, as defined by the Cartagena Protocol, would be another mechanism to assess the biosafety of plants intended for import.

Question 9—Currently, GE *Arabidopsis* spp. are exempt from interstate movement restrictions under part 340 because they are well understood and extensively used in research. Should the regulation of other similar GE plants be consistent with the regulation of GE *Arabidopsis* spp.? Should the exemption from interstate movement restrictions apply only to those products that meet specific risk-based criteria? What should these criteria be? What species and/or traits should be considered for this exemption? What environmental factors should be considered?

Most comments support the exemption of regulation during interstate movement for well-known, well-characterized, low-risk regulated articles. Some comments suggest that APHIS should grant exemptions for regulated articles that APHIS deems are unlikely to persist in the environment. Another comment suggests that movement and release permits (notifications) be integrated if the final destination of the regulated article is a field trial.

A few comments feel that the States have a right to know that the movement is taking place so that they can consider public health and safety issues.

Question 10—What are other areas where APHIS might consider relieving regulatory requirements based on the low level of risk?

Several respondents shared their ideas for reducing the regulatory burden in areas that they felt were low risk. Many of these comments suggested reducing data requirements for certain types of regulated articles. A summary of these views are presented below.

- Expedited reviews for renewals of existing permits, or multi-year permits, when there are no significant changes proposed in the permitted activity.
- If a crop-trait combination has been assessed by APHIS to be of low risk, there should be a ready and transparent mechanism to create and deregulate that crop-trait combination across multiple cultivars of that same crop.
- Deregulation should bridge to a deregulated antecedent organism using a notification procedure.
- APHIS should officially broaden its definition of non-transformed controls to include not only isogenic lines, but, also, near-isogenic lines and other appropriate genotypes or populations of the same species (e.g., appropriate and similar reference varieties, etc.).
- There should be exemptions from review or accelerated review of petitions for deregulation involving very low-risk biotech products. For example, products for which multiple, similar

antecedent organisms have been deregulated by APHIS, and/or for which familiarity is very high and prior environmental safety has been demonstrated by the trait-species combination.

- APHIS should allow renewal of authorized movement and release notification/permits. It would make the APHIS inspection and audit process more straightforward and transparent by allowing a single test area to continue to use one (or a few) APHIS permit numbers, rather than multiple overlapping permits each with a different number for the same group of regulated plants or plant types. The current 1-year-only permit system is ill-suited to perennials and is not efficient for permanent research facilities.
- APHIS could relieve regulatory requirements efficiently by instituting a new, additional type of site permit that would allow the applicant to test a variety of constructions made from a larger set or suite of user-defined genetic elements. Such a permit would be very efficient for early-phase trait development, proof-of-concept, or event-sorting studies. For example, an applicant would apply for release of any combination of identified promoters, genes (within a related gene or trait family), and termination sequences that could be tested in unspecified combinations.
- Low-risk GE plants should be exempted from interstate movement permit requirements on a case-by-case basis.
- APHIS should work with other Federal agencies to broadly deregulate GE tools for all crop species where scientific knowledge and experience suggest a high level of safety. These should include:
    - Selectable marker and reporter genes used widely in transformation.
    - Most *Agrobacterium* DNA, some of which is already known to be naturally present in plant genomes.
    - DNA from plant viruses used as promoters/terminators or other functional elements, or when used in non-functional form to suppress viral genes (and, thus, impart disease resistance).
    - General gene suppression methods such as antisense or RNAi.
    - Non-toxic proteins that are commonly used to modify development.
- The following exemptions of GE-associated genetic changes based on advances in genome and gene regulatory science:
    - Mutagenesis or pleiotropic effects associated with gene transfer and in vitro culture.
    - Random or directed transgene-imparted gain or loss of native gene expression.
- APHIS could develop a "best management practices" policy that would need to be agreed to by organizations seeking exemptions from requirements that specifies how growers of GE plants for field research should monitor, devitalize, and dispose of plants after completion of field trials.
- Determinations of transgene, vector, and flanking sequences, and transgene expression and toxicological properties should not be required for each insertion site prior to commercial use. Requirements for intensive characterization of insertion sites tend to limit commercialization to single-copy events due to expense, and such single-copy events, as discussed elsewhere, are not always desirable.
- Transformation-specific regulation is not warranted.

Question 11—What environmental considerations should be evaluated if APHIS were to move from prescriptive container requirements for shipment of GE organisms to performance-based container requirements, supplemented with guidance on ways to meet the performance standards?

Several comments suggest that the APHIS regulations are out of date. Some of these comments also suggest that APHIS should move from a prescriptive- to a performance-based standard for containers. Some of the issues cited include improvements in containers and specialized requirements of the material being shipped. Some of the considerations also suggested include (1) the potential for persistence in the environment should an accidental release occur during transport, (2) the likelihood that the regulated article will cross-pollinate with related weedy species or sexually compatible crop species, and (3) the potential safety hazard posed to any wildlife or humans who may come in contact with the regulated product in the event of an accidental release. A few comments suggested that APHIS should continue with a prescriptive regulation and avoid performance-based standards.

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Appendix D. Stakeholder Scoping Meetings

Representatives from stakeholder groups met individually with officials from APHIS' Biotechnology Regulatory Services in Riverdale, MD, in February 23, 25–27, and March 11–12, 2004. Participants were requested to respond to questions posed in APHIS' notice of intent to prepare an environmental impact statement on proposed changes to 7 CFR 340 (Docket Number 03–031–2, 69 FR 3271–3272). The following groups participated in the sessions:

- ArborGen
- Biotechnology Industry Organization
- Center for Food Safety
- Center for Science in the Public Interest
- Chlorogen
- Coalition for the Advancement of Biotechnology Based Perennial and Specialty Plants
- Consumers Union
- Controlled Pharming Ventures
- Dow AgroSciences
- Edmonds Institute
- Friends of the Earth
- International Paper
- MeadWestvaco
- Monsanto
- National Grain and Feed Association
- National Cotton Council of America
- National Food Processors Association
- North American Millers' Association
- Oregon State University (Prof. Steven H. Strauss)
- ProdiGene
- United States Public Interest Research Group
- Union of Concerned Scientists
- Ventria Bioscience

In general, each participant read a statement into the record, and their statement was followed by a question and answer period. Each session lasted approximately 45–60 minutes. The complete transcripts of the stakeholder meetings—over 500 pages of transcribed proceedings—are available on the APHIS–BRS Web site at: http://www.aphis.usda.gov/brs/stakeholder_minutes.html.

General Summary of Comments

Due to the diverse interests of the participants, the scoping comments raised during the stakeholders' sessions were equally diverse. The relevant scoping comments are listed below, grouped by topic, without attribution to a specific stakeholder.

Plants Producing Pharmaceutical or Industrial Substances

- Not all plants producing pharmaceutical or industrial compounds pose equal risks, and APHIS risk assessment processes should take this into account.
- The rules should provide an avenue to regulate plants producing pharmaceutical or industrial compounds after commercialization.
- Field tests for plants producing pharmaceuticals should be restricted to non-food crops.
- There should not be any open-air field trials for plants producing pharmaceutical compounds; they should be grown in contained facilities.
- Because food crops are so well understood and produce economically useful amounts of biomass, they must be available as hosts for pharmaceutical and industrial genes.
- The FDA food safety evaluation system for pharmaceutical plants is inadequate because it is voluntary.
- Considerations for crops producing pharmaceuticals should include the effect on herbivores.

Risk Analysis

- Some stakeholders preferred a tiered approach to risk analysis, while others favored a case-by-case approach.
- Confinement measures should be tested for adequacy and efficacy.
- GE technology should progress but not at the expense of the safety of the food supply.
- The overall size of a field test may not be relevant to risk; many small trials may be more difficult to manage, and, therefore, riskier than one larger test.
- Confinement systems should be redundant.

Regulatory Structure

- Regulations should have built-in flexibility to allow for developments in science and technology.
- Regulatory transparency must not compromise intellectual property rights or foster unfair competition.
- Conditional deregulation could raise unintended enforcement and liability issues.

Importation of GE Commodities

- Rules regarding commodity importation must not give foreign companies a competitive advantage.

Adventitious Presence (AP)

- There were requests for no tolerance as well as requests for tolerances to be set based on familiarity with the host plant and the compound produced by the plant.
- Coordination with FDA is necessary.

Organism-specific Concerns

- GE trees and turfgrass should be regulated differently from other GE plants.
- Insects should have separate regulatory status.
- APHIS should develop guidance documents for specific crops.
- Perennials may need special consideration.

Miscellaneous

- Nematodes may move genetic material from one plant to another.
- Exemptions for the movement of research materials should be limited to non-food plants.

Summary of Comments by Stakeholder Group

The following section summarizes a few representative points made by each stakeholder group. The complete transcript of each meeting is available online at the link provided.

ArborGen

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Arborgen.pdf

- Believes that the current system works well; would like to see flexibility to address new crop and trait combinations
- Create risk categories based upon trait and species combinations, on a case-by-case basis, as opposed to broad, general categories (like 'trees').
- Would like a clearer definition of 'familiarity'—scientific literature and professionals may show a great deal of familiarity with some applications with which APHIS is relatively *un*familiar.

Biotechnology Industry Organization

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Bio_Meeting.pdf

- Advocates the term 'approval' as opposed to 'granting non-regulated status;' previous lines granted non-regulated status should be grandfathered into the new system.
- Wanted clarification on whether the *intended use* of a crop would put it into a risk category (e.g., pharmaceutical-producing crops); some crop-trait combinations in such categories might be lower risk than others.
- Need a policy for AP now; should be considered for imports as well as exports.

Center for Food Safety

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Center_for_Food_Safety.pdf

- Restrict biopharmaceutical crops to restricted conditions (greenhouses/underground, limited geographical areas).
- Wants the ability to list specific GE crops as noxious weeds
- Wants field tests of biopharm crops never to be categorically excluded from NEPA; clarify terminology related to categorical exclusions.
- Several recommendations to update Confidential Business Information (CBI) policy.
- Trees and grasses should have a separate category of regulations.
- Insects raise a need for separate regulatory status.
- No tiered categories of risk categories; each event requires the same review.
- Minor risks should be characterized prior to commercialization.
- No food crops should be used for pharmaceutical production.
- No acceptable AP without a safety review.

Center for Science in the Public Interest

The transcript of this meeting was lost by the transcription company. The points below have been summarized from notes taken during the meeting.

- Wants greater access to APHIS documents, more opportunity for public participation.
- Supports commercialization under permit to allow continued oversight.
- Supports more careful review of CBI justification by APHIS and challenge when appropriate.
- Tiered risk system should differentiate between non-food crops and food crops with non-food uses.
- Food safety assessments and AP policy should be FDA's responsibility.

Chlorogen

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Chlorogen.pdf

- Support risk-based tiered approach to permitting and sub-tiers for PMIs and PMPs.
- Support process for keeping PMIs and PMPs under regulation even after commercialization.
- Do not support an AP policy for products not intended for food or feed.
- Supports more transparency to the public, while protecting intellectual property rights and competitiveness.
- Wants better communication between APHIS and applicants, and APHIS and State officials

Coalition for the Advancement of Biotechnology Based Perennial and Specialty Plants

Transcript:
http://www.aphis.usda.gov/brs/stakeholder/Coalition_for_Advancement_of_Biotech.pdf

- Wants guidance documents developed for additional crops, such as perennials.
- Having a simplified way to renew annual notifications would help.
- Assess risk case-by-case and by trait and species combination.
- Investments in perennials are long-term; investors will be concerned if there is a possibility that risks or status could change from year-to-year.
- Burdensome for companies to push new species through the process of being added to the list of 'exempt' species.

Consumers Union

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Consumer_Union.pdf

- Would like development of regulations to cover all GE insects.
- There should not be a 'low risk' category because there could be unintended effects even with low risk organisms.
- Supports some regulatory oversight after commercialization.
- No allowance for AP of unapproved varieties.
- Supports environmental assessment of importations of viable plant materials.

Controlled Pharming Ventures

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Controlled_Pharming_Ventures.pdf

- Discussed a new business venture involving production of GE plants in an abandoned limestone mine in Indiana.

Dow AgroSciences

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Dow_Agro_Sciences.pdf

- Need AP policy which should be coordinated with FDA; concern for international implications.
- Supports current stringent standards for PMP and PMICs.
- Supports performance-based container requirements.
- Don't want new rules to affect products overseen by Center for Veterinary Biologics.
- Concerned about having enough data on novel proteins for early FDA consultation.
- Limiting acreage may not help to manage risk; producers might increase risk by planting in many smaller plots than a few larger plots.
- Does not advocate limiting PMPs/PMICs to non-food crops.

Edmonds Institute
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Edmonds_Institute.pdf

- Recommends examination by the Edmonds Institute on GMO biosafety.
- Wants more transparency in the coordinated framework, how agency makes decisions.
- Concerned that CBI claims reduce transparency. Advocates long-term economic analysis of any AP policy.
- Concerned that CBI claims reduce transparency. Advocates long-term economic analysis of any AP policy.
- Supports PMP production indoors with strict containment standards.
- Wants to close any regulatory gaps so that everything genetically engineered is regulated.

Friends of the Earth
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Friends_of_the_Earth.pdf

- Does not support establishment of AP policy; APHIS regulates experimental crops and are evaluated for environmental effects, so to allow for any presence before the petitioner applies for deregulation prejudges the outcome.
- Use strip tests to confirm compliance to permit conditions.
- Concerned with contamination of seed supply.
- Low-risk categories should not be exempted from permit conditions.
- Supports continued regulation as opposed to deregulation in some cases, and/or the ability to cancel deregulation.
- Supports a ban on all outdoor plantings of food crops containing PMPs.

International Paper
Transcript: http://www.aphis.usda.gov/brs/stakeholder/International_Paper.pdf

- Believes risk should be assessed on a case-by-case, crop by trait basis, including trees.
- Does not support regulation of all non-viable material.
- Supports expedited review for imported GE commodities.
- Supports the use of performance standards for shipping containers.

Mead Westvaco
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Meadwestveco.pdf
- Assess risk on a case-by-case, trait/species basis; don't lump all trees together in one risk category.
- Discussed various types of ecological forest management systems.

Monsanto
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Monsanto.pdf

- Considers AP policy to be an urgent need.
- Supports oversight that is proportional to the level of risk.
- Wants the ability to be flexible in the size of field trials for various traits.
- Resists the idea of commercialization under continued oversight, monitoring.
- Might support post-deregulation adverse effects reporting.
- Concerned that deregulation/approval is tied to both the product and the petitioner.
- Wants the EIS to include an economic analysis of regulatory costs to industry.

National Grain and Feed Association
Transcript: http://www.aphis.usda.gov/brs/stakeholder/National_Grain_and_Feed_Assoc.pdf

- Does not support reduced permit requirements for PMPs due to export concerns.
- Concerned how conditional approval would be interpreted by export markets.
- Permit conditions/requirements for PMPs should be different than food applications.
- Food safety assessment is irrelevant to marketing issues.
- AP policy is difficult; United States needs a policy, but most markets have zero-tolerance for unapproved varieties.
- Supports expedited review of imported GM varieties if approved in exporting nation.

National Cotton Council of America
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Natl_Cotton_Council_of_America.pdf

- Concerned that companies that produce an early product may end up subsidizing companies that produce later ones, if data requirements are lowered for "familiar" crops.
- Cautions against arbitrary familiarity standards; novel traits should not be considered familiar.
- Does not support conditional approvals, due to marketing issues.
- Supports stringent regulation and monitoring of PMP/PMIC crops.
- Imports should be evaluated with the same stringency as crops produced in the United States.
- If there are exceptions (such as *Arabidopsis*), they should be fully deregulated.
- Supports shipping container standards.

National Food Processors Association
Transcript: http://www.aphis.usda.gov/brs/stakeholder/Natl_Food_Processors_Assoc.pdf

- Very concerned about issues associated with commercialization of PMP crops.
- Suggest issuing 'letterhead statements' about which crops APHIS has deregulated or not, especially regarding PMPs.

- How would APHIS regulate 'botanicals,' that is, crops with enhanced nutritional properties, but not necessarily a PMP/PMIC?
- Support keeping PMP/PMICs under regulation even after commercial production.
- Encourage the use of HACCP protocols for confinement/commercialization.
- Concerned about liability if PMP/PMICs enter the food supply.

North American Millers' Association

Transcript: http://www.aphis.usda.gov/brs/stakeholder/North_American_Miller_Assoc.pdf

- Suggests having a scientific meeting to determine how far viable corn pollen travels.
- Wants regulations to be science based but concerned about human error.
- Wants a large increase in compliance and enforcement.
- Concerned about PMPs in food crops like corn, especially in corn production areas.
- Concerned about liability of companies producing PMPs.
- PMPs should have either full food-safety approval or a very low acceptable AP level.

Prof. Steven H. Strauss, Oregon State University

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Oregon_State_University.pdf

- Important that regulations are not too expensive for small companies and public researchers.
- Support a science-based three-tiered risk system; low-risk tier could be exempt from regulation.
- Trigger for regulation should not be process, but characteristics of the product.
- Should not deregulate on an event-by-event basis.
- Wants an AP policy to protect developers.
- Allow unregulated interstate movements for most classes of GE crops.
- Deregulate a list of common genetic engineering tools, like promoters, etc.

ProdiGene

Transcript: http://www.aphis.usda.gov/brs/stakeholder/ProdiGene.pdf

- Regulation should be based upon risk, not the class or products based upon end-use.
- Everything should start in the high-risk tier until evidence supports a lower risk.
- Some PMP/PMIC crops might be deregulated if they are low risk..
- Supports the idea of long-term regulation under a 'compliance contract.'
- AP policy should consider not just hazard, but also exposure; proposed such a model.

United States Public Interest Research Group

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Public_Interest_Research.pdf

- Complained about difficulty getting information from APHIS.
- PMP/PMIC should be restricted to non-food crops; no open field tests.

- Questions definitions of risk and their implications for regulations, e.g., "minor unresolved risk," "low level of risk."
- Need more monitoring and testing, none currently done by government.
- Need better quality control for confinement.

Union of Concerned Scientists

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Union_of_Concern_Scientists.pdf

- Support adoption of the noxious weed authority from the Plant Protection Act.
- Support a risk-based tiered permitting system.
- Don't support the idea of AP policy being tied to pre-testing food safety evaluation.
- Support lessening of regulation of interstate movements, particularly for research.

Ventria Bioscience

Transcript: http://www.aphis.usda.gov/brs/stakeholder/Ventria_BioScience.pdf

- Want USDA to establish a risk-based AP policy.
- Support a risk-based tiered permitting system.
- Some criteria for risk: host biology, impact of gene, expression of selectable markers, quantity of active material, selective advantage of material in host plant.
- Do not intend to seek deregulation of PMP/PMIC crops.

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Appendix E. NADSA–USDA Conference, June 17–19, 2004

The National Association of State Departments of Agriculture (NASDA) met with APHIS' Biotechnology Regulatory Services on June 17 and 18, 2004, in Washington, D.C., to discuss APHIS' proposed revisions to its existing regulations. The 60 participants discussed the specific questions raised in a notice of intent to prepare an environmental impact statement on proposed changes to 7 CFR 340 (Docket Number 03–031–2, 69 FR 3271–3272). The main points offered by meeting participants, as summarized by APHIS staff attending the meeting, are presented below.

The Regulation of Crops Producing Pharmaceutical Compounds

Encouraging Industrial Production: State and Federal Policies

Representatives from several States were optimistic about the present and future business activities of the plant-made pharmaceutical (PMP) and plant-made industrial compound (PMIC) industry. Companies have been inquiring about PMP/PMIC crop production in their States, and the States were also seeking to contact additional technology companies. Policies to encourage production of specialty products were proposed as useful for some States. Growers also recognized possible opportunities and were interested in initiating and furthering these types of projects. The State representatives said that the public did not seem to have any objections to these plant manufactured products, or at least hadn't voiced any. Companies had not been complaining about existing regulatory burdens, either.

Some said APHIS should continue to effectively regulate field tests, but should have a "forward-looking attitude" and not attempt to over-regulate (and, thereby, inhibit progress of an industry). New restrictions shouldn't be set if the standards could not be readily attained. Reasonableness of confinement plans was contrasted with imposing excessive burdens on industrial production. Some of the representatives noted that they were not familiar with the confinement standards, but if they exceed AOSCA standards, they are probably adequate.

Concerns About Permits and Conditions Set for Field Testing

Some States did not want to allow flexibility in permit conditions. Some would rather move in a more restrictive direction, especially when there were possible impacts on humans. Due deliberation for individual releases might well result in enhanced confinement standards. More stringent conditions should be allowed if significantly increased toxicity or allergenicity were apparent. If the industry is taking new steps to insure confinement and quality, these changes should be included in the new regulations. If industry were only using minimal restrictions for safety, they should consider additional restrictions. Concerns were expressed about new and small companies: they may not adhere to applied restrictions or conditions due to inexperience

or lax attitudes about safety issues. Other concerns were raised about contamination by PMPs/PMICs, especially in putting conventional variety growers at risk.

Concerns were expressed about the lack of science available for determining proper isolation distances. Extra measures of redundancy were thought useful, especially to refute opponents of the technology. Some saw gene flow as an important consideration for regulations, and others noted antibiotic resistance as an issue.

Some inherent differences between PMP and PMIC crops may require differences in how these are regulated. That is, PMICs are more likely to be produced on large acreages, but PMPs may well be produced on only small acreages. These differences would need to be acknowledged in conditions assigned to field production.

Long-term Concerns for Effects of PMP/PMIC Crop Policy on Markets

Some States had limited experience with PMP/PMIC crop projects, and the possibilities of mistakes and harm to markets was raised. At present, there is often no authority in the States for dealing with GE crops. Some said that State regulations regarding PMP/PMIC crops should be adopted. Some are looking for guidance to deal with the issues surrounding these plants. Some States have a plant pest authority, although it varies by jurisdiction. Nevertheless, these could be the basis for some additional State oversight if it would not conflict with Federal authority. Some were concerned that certain products may not be plant pests but were, instead, "market pests" and that some balance should be struck between science-driven restrictions and market-driven restrictions. Confidence in the measures taken should be instilled in the public once the appropriate conditions are designed. While companies could assist with this, they have, so far, not been helpful.

Use of Contained Facilities for PMP/PMIC Crop Production

Some thought that producing PMP/PMIC crops under only completely contained conditions may be unreasonable, although there could be some cases where this protocol should be required. Some products might be produced economically in a greenhouse (or other completely contained facilities). Some thought that PMP plants should be tested first in contained facilities before being allowed in a field release. Perhaps small-scale testing should precede larger scale production. Others responded that APHIS should keep in mind that the PMP production process is aimed at speeding up synthesis of these PMP products—an "instant factory"—and that additional steps might reduce the advantages. Finally, some noted that existing performance standards should be adequate to confine PMP plants.

Public perception was considered quite important, and public perception might motivate more stringent requirements. Growing conditions need to be correctly (scientifically) assigned and also generally perceived as adequate for confinement. However, one State suggested that regulations could not be based on science alone, but also should consider what was physically possible, and administratively possible, too. If the protocols were good ones to begin with, then compliance with them should be expected. Others said that all conditions for field tests should

be determined with science considerations, rather than public perception. For both the growers and the public, conditions of the field production should be acceptable ones. Finally, criteria for evaluating the risks should be well-developed and transparent.

Use of Only Non-food Crops to Produce Pharmaceuticals

If PMP production could be accomplished in non-food crops, industry could move in this direction. However, if APHIS required that only non-food crops could be used for PMP production, some companies could be put out of business. Regulatory authorities shouldn't be overcautious but might encourage the use of non-food crops like tobacco. Others noted that tobacco is actually a consumer commodity, but, nevertheless, might provide a safer production vehicle than other actual food crops. Still others thought tobacco may be as risky as corn, soybean, and wheat. Another stated that alternative host plants should be encouraged.

Science needs to be considered in such decisions (e.g., exclusion from certain food or feed crops), but some regulatory flexibility needs to be exercised, too, which includes permitting the expression of PMP products in food or feed crops. Alternatively, regulations could be made more stringent for food crops than for non-food crops. More public acceptance could be found for production in non-food crops and in crops without wild relatives.

Other types of restrictions might be pursued. For example, industry could be encouraged to produce pharmaceuticals in plants that were not open-pollinated. Some would have a greater comfort level in PMP/PMIC crops if the expression were confined only to seeds. Some States suggested broadening their role in both assignment of conditions and mitigation. While the Federal government coordinates with the biotech companies to determine conditions and, together, may mitigate possible failures involving plants or plant products, the States could also do this work.

New Oversight Mechanisms for PMP/PMIC Crop Production

Some States would support some kind of "commercialization permit" for PMP/PMIC plants. One State thought that a contract system might be helpful so that States (or even counties) could have greater control over possible gene flow. Participation issues were important to some States. If any new system were adopted, there would have to be consideration of a company's past performance and how it might change the production scheme or other protocols from the permit based system. The States would need to be more involved in setting up the system and periodically audit performance. Any new mechanism for PMP/PMIC crops should keep the "gene owner" accountable under the terms of a contract.

Any new regulatory mechanism should be extremely conservative, but it may be premature to try to set up a new one. The public may not be ready for any process of pharmaceutical production in plants unless it is conducted under a permitting system. Some States noted that they would like a continued permit system with regulatory oversight.

Some States would be very uncomfortable with any type of deregulation of PMP/PMIC crops. If deregulation occurred, there would need to be some mechanism to maintain continued control over these crops. Inspections should remain under USDA control, especially while any system was new. One State pointed out that the public expects accountability in regulation, not efficiency.

Concerns were expressed about any new regulatory framework unless they necessarily include more frequent assignment of unique confinement conditions on a case-by-case basis. Agency guidelines may need to be provided to the producer if their own SOPs were lacking or inadequate. This might bring complaints about unfairness in the way that the regulations were applied. The opposite strategy, in which all permit holders would abide by more general protocols, may also be perceived favorably by the public.

Questions were raised about who would do the inspections under a new system and their qualifications. The States would like an inspection reporting mechanism that automatically reports to the State containing the release site. They also wanted to have planting reports sent to them since the State might need to know which sites are to be inspected.

A list of the characteristics of a new system for oversight of PMP/PMIC crops should include:

- Equal enforcement of biotech regulations of both States and Federal governments.
- Flexible regulations that keep up with the technology.
- Provision of guidelines for companies that do not have adequate SOPs.
- Training for State regulators to be able to answer questions from the public.
- Initiating an extremely conservative system.
- Provision of clear guidelines for the State regulators.
- Involving the State regulators, including inspectors.

Special Concerns From States

When asked to concur on a permit, States would like some kind of workshop to train them in what issues to consider. Because many are not molecular biologists, presenters would need to make allowance for that fact in any workshops. Some would like to establish a new mechanism or relationship with the States and Federal government for field testing. For example, an opportunity for the State to discuss local concerns should be offered before field trials are laid out by the company. Others noted that the State representatives should be included in the relationship more as partners than does the relationship at present. Without good Federal-State partnering, establishing credibility in the system will be a difficult task. Good partnering should also include accompanying all APHIS inspectors on their assignments.

One question raised was, “What can the State do when there are special State concerns over a field test?” APHIS replied that it has always allowed supplemental conditions to be placed on a permit, trying to balance the needs of industry and the States.

A second concern was for issues arising over CBI. Here the States noted that because CBI prevented full knowledge about the details of field testing, the States could not assure the citizens that rigorous reviews had been done. One State noted that CBI deletions provided a credibility problem for them, namely how can the States say they're reviewing information that is not provided? Could some abstract be provided that was pertinent to the tests when CBI information cannot be divulged? They would like to know about the genes and intentions of the developers for the field tests: whether the active principle is expressed only in seeds or other specific tissues should be shared by APHIS, as well as how the material will be used (what parts are harvested, how they are extracted or activated, what products they will become).

Compliance issues were deemed important, and, if the protocol called for 28-day temporal separation, for example, there should be records showing the dates of compliance. Without verification, protocols and conditions are of little value. The States should be called on to help in compliance efforts because they have better knowledge of the crops and situations.

Concerns were expressed for the availability of APHIS inspectors. APHIS replied that it is developing a Memorandum of Understanding (MOU) with PPQ to assure the cooperation of PPQ in inspection efforts. Also, APHIS is developing a program to certify State inspectors to do the inspection work.

Adventitious Presence

APHIS should be concerned about adventitious presence (AP) especially because it can be detected at very low levels. When undesirable AP is found, there must be a mechanism in place for assuring the public of the safety of the gene product. Criteria for AP have been set in some places, such as allowances by the EU of 0.3 percent of GE in non-GE seed, and as much as 0.9 percent in food or feed commodities.

Concerns were expressed about the absence of U.S. policies regarding AP because, without these policies, decisions about AP will necessarily be made abroad. A second consequence of no AP policy is that other countries will send us commodities without any U.S. input into their AP. Additional outcomes of inaction were discussed. For example, other economies may produce the very products developed here, and an absence of tolerances for presence of AP will drive their production abroad.

If the United States sets AP standards, the rest of the world will be attentive since other countries would need to meet any new U.S. requirements. A U.S. decision for AP tolerances would be a precedent-setting international model. APHIS needs to formalize U.S. policy, assure that it is appropriately transparent, and, thereby, satisfy the concerns of U.S. trading partners. When others are confident in our system, then the United States will be able to meet existing export market needs.

Expedited Review Process for Unapproved Commodities

If the United States sets tolerances or exemptions, they should be set on a case-by-case basis. Several States did not favorably view the setting of numerical, across-the-board tolerances. One proposed exempting families of traits as allowable AP. Others proposed setting AP tolerances for each crop. If exemptions were permitted, it should be done because APHIS or FDA has taken responsibility for the commodity.

Zero tolerance was recognized as an unrealistic policy by one State representative. Another, knowing that tolerances will not necessarily be found acceptable to the public, suggested a second option: rather than develop a system of exemptions and tolerances, APHIS should consider setting extensive protocols for quality assurance. North Carolina developed one for production of non-GE tobacco with basic similarities to those for organic crop production. Compliance with approved protocols assured GE-free status, and no direct testing was done.

FDA approvals of tolerances would be helpful, and may be possible, since FDA currently specifies thresholds for fungal presence in foods. Is APHIS then moving toward setting a threshold? Two States proposed some sort of testing regime, one able to establish the safety of exempted proteins. In 2002, FDA proposed establishing, in some cases, a process for early food safety assessment. Is APHIS planning to force applicants into a pre-approval meeting with the FDA? APHIS suggested that petition applicants could be compelled to submit food safety assessment documents to FDA. Simultaneously, they would submit an environmental assessment to APHIS. If APHIS approved both assessments, designation of exempt status for a gene product would be made if it were to be found as AP.

If a product has been approved elsewhere, such as in Canada, then that approval should be an adequate basis for our acceptance. If the United States has sufficient confidence in another country's regulatory system, then the United States should routinely accept their approvals. However, if a product is unapproved elsewhere, then the United States should have concerns about accepting it here. The United States should always retain its concern for possible environmental impacts in any approvals that are finalized.

Tolerances

If APHIS decided to set AP tolerances, two audiences may receive them adversely. The first is the international and export markets, and favorable approval by these buyers is highly critical for growers and marketers. The second is the public. Will they accept the presence of low levels of AP without criticism? The public will want to know whether the food is still safe even after tolerances are set. While the food may, indeed, be safe, a more difficult question might be, "how safe is it?" If some exemptions are set, then the policy should be thoughtfully presented to the public. One can envision that a gap may arise between scientific acceptance and public acceptance. One commenter suggested that it is perception that drives the market and that scientific facts would not make a difference in what the public expected.

Disapproval was expressed for blanket exemptions of unapproved events. One reason against exemptions is that some growers or middlemen will always be pushing against reasonable limits and allowing incorporation of something unacceptable. A second reason is that such exemptions would provide easy targets that anti-GE activists could take aim at. Another thought is that there should be no exemptions, but that the whole process of the U.S. system should be brought to consider each AP component. Standards for importation should be no more lax than standards used for products produced here. However, stricter standards for imported commodities should not apply either.

Representatives raised questions about the effects of these policies on trading partners. Would USDA need to rely on the trading partner's opinions for setting the policies for exemptions? Others thought that the commodity groups should themselves address this issue; yet others suggested that these groups were the ones asking for the Federal policy. Still others wanted to know why our present standards should be relaxed. By suspending the full process of review, the concern was that our producers may become less competitive. Why should the United States allow a foreign producer some exemption that their own system may not allow them? What is the present process for AP in other countries? APHIS noted that our producers must meet those countries' standards, and that some do not permit any GE, or may require a certificate for import (China). The United States has allowed entry of unapproved canola for processing here.

Concerns were raised about accepting something that was "not intended for planting" but was, nevertheless, viable. How would you prevent something from being planted if it were viable? If any imported commodity is viable, APHIS should have the same concerns as it would have for a Monsanto product produced here. However, if it can't grow here, then accepting it would not be a problem.

Some were concerned about the means for testing the presence of unapproved events. Because the allowed levels might likely be quite small, the sampling procedure would need to be very well thought out and carefully conducted. The testing locations would also need to be considered, and could include random testing within the general commodity or, alternatively, be limited to fields near the test sites, or to grain elevators near test sites. One State representative also wanted a requirement for testing of fields containing any exempted pharmaceuticals. The focus for regulation of field testing is determining the needed safety criteria in the field. A question was raised about the level of importing that would trigger an analysis of AP content: would research-scale as well as commercial-scale imports be assessed?

Exemptions for Research Organisms

One State representative agreed that exemptions should be specified, but posed the question of how it could be done. Another raised the issue of adequate detection methods and wondered whether it was possible to write regulations when the methods for detecting AP are continually changing. Finally, if decisions were to be made, then an effort should be made to describe the need to the public.

Some wanted the exemption to be explicitly laid out in the regulations and some did not. While some thought that written regulations would be useful, others thought that specifying anything too precisely would be cumbersome. There should be a case-by-case allowance for AP, and no general level set except for generally recognized as safe (GRAS) substances. It would be a mistake to spell out a single level. If a component was GRAS, then low-level presence could be accepted, but if not, then an FDA consultation would need to be arranged. These consultations should remain voluntary. Companies that were serious about the acceptance of their product would have gone to FDA already, early in the process. If USDA were to approve the presence of a PMP crop before FDA approval, it would be seen as an ill-advised decision. Questions were raised about GRAS and it was noted that, although a material may have GRAS status, the status may be awarded for a single use and not for its presence in all food materials or at all concentrations. Early on in the development of PMPs, a company is not likely to seek GRAS status. A problem might exist because of detection methods, which are constantly changing, and these might need to be included if a regulation was written.

The representatives raised a number of other issues. Would large scale production be needed before FDA would do a consultation? Should APHIS compare AP to pesticide presence in a non-target situation? Are there levels which might be acceptable? Can some constituents be undesirable but not a health threat? Setting AP thresholds might allow growers to just barely meet the standards, without doing anything exceptional, to assure minimal presence in food or feed.

Certain advantages were obvious if FDA were to do a consultation before AP levels were set. For setting field testing protocols, less stringent conditions should be based on acceptance of food safety by FDA, and, if none were given, then protocols suitable to higher risk materials would be required.

Growers should begin production using every standard procedure that would contribute to confinement. Then, if something happened, let the grower explain what went wrong. Another suggested he could not understand the term "unavoidable" circumstance. There is always the potential for an oversight. If APHIS keeps a policy of 0 percent AP as the goal (even if it is unattainable), then APHIS should set protocols for attempting to have 100 percent containment.

If unapproved AP were reported or detected, what is the appropriate response? APHIS should try to avoid giving penalties for accidental AP if the incident was truly unavoidable. APHIS really needs a balance between promoting good production processes and preventing unwanted outcomes. In the end, the United States still need acceptable results, however. The good practices selected for the production process should help to attain the chosen threshold. Again, the desire is to have a marketable product at the end of the farm production effort.

The question was raised, why should there be one standard for seed for planting (deregulation) and another for seed arriving as commodity (exemption)? In the future, there may be many commodities containing plant parts that APHIS has not reviewed. If they have been reviewed elsewhere already, would it be worth United States resources to repeat such a review? Other countries would follow our lead if APHIS accepted foreign standards, and, thus, by example,

steer them from a new local review of U.S.-approved products. Should there be an environmental review even if the only release would be accidental? APHIS should remember that environmental reviews are also used to leverage trade issues. The United States would need to have a reciprocal set of agreements. Better still would be just a level playing field—reciprocity is important. Otherwise, other countries can use lack of agreements as trade barriers.

Topics Related to APHIS Authority

Scope of Current APHIS Authority

Although APHIS is currently addressing potential environmental impacts under present authorities, there is no reason not to expand this authority. However, will invoking additional authorities require additional resources to implement them?

There is no way to predict what technologies may be developed in the future so it's wise to broaden APHIS' authority. It is better to be proactive than to find that you need expanded authority later. Using the noxious weed definition from the Plant Protection Act would allow additional categories of GE products to be evaluated.

The use of the phrase "noxious weed" could be used against us because of the emotional impact that it carries. Although the noxious weeds designation has a negative connotation, it also has a precise legal status. APHIS would gain more than it lost by using the noxious weed definition.

Biological Control Organisms

Doesn't APHIS–PPQ already regulate biocontrol organisms? Why should two programs regulate the same organisms? If PPQ had a GE biocontrol organism, wouldn't they consult with APHIS anyway?

Exemption of Low-risk Items

The exempting of low-risk items from the permitting process should be decided on a case-by-case basis. One of the beneficiaries of new exemptions would be researchers, but APHIS should note that the States often have problems with compliance of such individuals in educational institutions. Researchers and small companies often do things without following designated procedures. Others agreed with the need for exemptions, but were insistent that APHIS should allow these exemptions only if there were indeed a low risk, and it was accurately determined to be low risk. If the regulated article were clearly not a high risk, the issue of exemptions would often not be a problem.

While a system of exemptions has some merits, the public still wants to know what has entered the State. Issues of risk assessment were considered to be variable from one State to the next. Risks must be evaluated by the perceptions of the public in each of the States. Thus, decisions on exemptions would need to be coordinated between States. The notification process must remain the same between States, even if the assessment process differs.

Establishing Risk-Based Categories

The three APHIS-proposed categories should be broader. Tiered assessment processes should also be considered. These tiers could be based on the three categories, but one representative proposed that APHIS should add as many tiers as necessary.

Yet another opinion proposed that the number of categories is not critical, but multiple categories were probably needed. Some mechanisms should be incorporated to add additional categories without any formal rulemaking, but only on evidence of hazard and exposure. Still others suggested that few categories should be created, and they should be broad, inclusive categories.

Additional Issues

Problems in Exchanging Documents With APHIS

APHIS mailing lists need to be updated with current addresses. Some things have been sent to incorrect cross-town addresses, and delivery was extremely slow to the correct address. Some items are FedEx'ed when they could be sent by fax, as similar items are sent. Regular mail is an acceptable means for sending permit concurrences.

A fax black hole exists where documents have to be faxed to APHIS multiple times.

APHIS and EPA Field Tests

Experimental Use Permits (EUP) field test locations may have a similar USDA permit but sometimes do not. However, EUPs contain information about things that are deleted in the APHIS permits. The two agencies should cross list them so they can match them up, and so do not inspect sites twice.

Permit Conditions

For specifying permit conditions, growers suggest that degree days should be used, not calendar days. Because temperature greatly impacts growing conditions, these are highly inaccurate as compared to events calibrated in calendar days.

Concerns About the Permitting Process

What if the State doesn't sign off on a permit? If the failure to sign is a consequence of the State not desiring to approve the conditions of the permit, then APHIS should be apprised of the concern so as to resolve it.

The State may not have enough information to approve or deny the application. What, for example, is if something that is described in the permit application as a "novel protein?" From this information, it is hard for the state regulator to comment on the permit. Another

representative said that it was ridiculous to ask the States to concur on permits, because they often do not know exactly what they are concurring with.

Suggestions for the Permitting Process

For PMP/PMIC crop permits, APHIS should give the States more than 30 days to concur. States need more time to consult with reviewers, such as university personnel, and they cannot be recruited on short notice.

There are problems with the adequacy of information provided by the Federal government. For example, information about planting site locations in notifications is inaccurate. In other cases, the State may plan an inspection but then finds out that the planting was not done as stated on the notification. Often there is not adequate contact information about the notification holders. The lack of access to CBI information also makes the process difficult. In other cases, the State had a concern about conditions on the permit and only after much interaction were these concerns addressed. Sometimes there is an interstate or import quarantine at issue which is not addressed by APHIS. While the burdens on the State are not excessive at present, should the number of permits rise, while the State may simultaneously experience financial exigencies, a future burden may be incurred.

The State representatives want to attempt to quantify risks, if possible, and avoid using the reasoning of the precautionary principle, especially if that means suspending permits when complete certainty for the safety mechanisms could not be guaranteed.

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Appendix F. Issues Associated With Importation of Regulated Articles into the United States

Trade agreements such as the North American Free Trade Agreement (NAFTA) (http://www.fas.usda.gov/info/factsheets/NAFTA.asp) and the General Agreement on Tariffs and Trade (GATT) (http://www.wto.org/english/tratop_e/gatt_e/gatt_e.htm) have increased agricultural trade and expanded the crucial role for the U.S. Department of Agriculture's (USDA) Animal and Plant Health Inspection Service (APHIS). APHIS facilitates agricultural trade for both importers and exporters, and its Plant Protection and Quarantine (PPQ) unit is central to the successful flow of healthy commodities into and out of the United States. APHIS safeguards agricultural and natural resources from the risks associated with the entry, establishment, or spread of animal and plant pests and noxious weeds. Its safeguarding role ensures an abundant, high-quality, and varied food supply, strengthens the marketability of U.S. agriculture in domestic and international commerce, and contributes to the preservation of the global environment.

APHIS' Role in the Importation of Agricultural Products

Over the years, Americans have come to count on a diverse array of agricultural products. In order to fulfill these needs, the United States imports commodities from around the world. For example, in FY 2003, the United States imported $45.7 billion dollars worth of agricultural products. By far the largest U.S. agricultural imports are horticultural products, which, by 2002, accounted for half of all U.S. agricultural imports. Horticultural products include fruits, vegetables, nuts, wine, malt beverages, and nursery products. Many of these imports come from two leading suppliers, Canada and Mexico. Animals and animal products from Canada, Mexico, and Oceania are next in importance among U.S. agricultural imports. Tropical products (such as coffee, cocoa, and rubber), which the United States does not produce in significant quantities, are the third-largest U.S. import group.[1]

However, some foreign countries have agricultural pests and diseases that do not exist in this country. These pests and diseases can cause devastating damage to U.S. agriculture if introduced. Consequently, APHIS strives to ensure that imported products are free of harmful pests and diseases. APHIS does this by regulating the importation of agricultural products with phytosanitary (plant health) certificates, importation rules, and inspections.

Anyone wishing to import certain plants and plant products into the United States is required to have a phytosanitary certificate. The intended purpose of a phytosanitary certificate is to expedite the entry of plants or plant products into the United States while protecting American agriculture. A phytosanitary certificate is an official document issued by an exporting country, which certifies that the shipment has been inspected and meets the phytosanitary regulations of the United States. In addition, the phytosanitary certificate indicates that the shipment is free of

[1] From the USDA Economic Research Services's web page: http://www.ers.usda.gov/Briefing/AgTrade/overview.htm#imports.

pests and diseases that do not exist in the United States.[2] The use of phytosanitary certificates is prescribed for the movement of such commodities under the International Plant Protection Convention, to which the United States is a party.

The National Center for Import and Export (NCIE), a part of APHIS' Veterinary Services program, also plays an integral role in APHIS' mission of protecting U.S. agriculture. NCIE regulates the import and export of animals, animal products, and biologics, and monitors the health of animals presented at the border. NCIE's animal health experts work closely with other Federal agencies, States, foreign governments, industry and professional groups, and others to enhance international trade and cooperation while preventing the introduction of dangerous and costly pests and diseases. Generally, a USDA veterinary permit is needed for live animals and materials either derived from animals or exposed to animal-source materials. These materials may only enter the United States through a small number of ports and the materials are inspected upon arrival into the country.[3]

Balancing Homeland Security and Agricultural Trade

On November 21, 2002, President Bush signed legislation creating the U.S. Department of Homeland Security (DHS) to unify Federal inspection forces and protect our nation from a new host of terrorist threats. Programs and staff from more than 22 Federal agencies were consolidated into the new department, including portions of USDA–APHIS. Although DHS is now responsible for conducting inspections at our nation's borders, APHIS continues to determine which agricultural products can enter the country and which products pose a risk and should be kept out. Through risk assessment, pathway analysis, and rulemaking, APHIS continues to set agricultural policy that is then carried out by DHS.

Importation of Genetically Engineered (GE) Commodities

For the past decade, the United States has been primarily a producer and exporter of products of agricultural biotechnology, two primary examples being soybean and corn varieties developed in the United States. APHIS has deregulated many other products that may be produced and used domestically or exported. Currently, few nations are exporting GE agricultural products to the United States, and the United States remains a net exporter of these products. However, as research and development of new GE products increases worldwide, and other countries approve agricultural biotechnology products for domestic use or for export, the United States will likely see an increase in requests to import GE organisms for research or for commercialization, both as seed for planting and for use in food and feed. As APHIS considers revisions of its regulations, the agency needs to ensure that it has appropriate oversight over imported products, as well as products produced domestically, and to ensure equitable treatment of imported products.

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[2] From the USDA APHIS PPQ web page: http://www.aphis.usda.gov/lpa/pubs/fsheet_faq_notice/fs_aphisimport.html.

[3] From USDA APHIS Veterinary Services Web page: http://www.aphis.usda.gov/vs/ncie/.

Current Status

GE agricultural products imported into the United States are subject to the same APHIS–PPQ regulations covering the importation of non-engineered varieties, such as 7 CFR §§ 319–37 (covering importation of plants and seeds for planting) and 7 CFR §§ 319–56 (covering fruits and vegetables imported for non-propagative use). Therefore, the commodity would have to be "allowed" for importation from a particular country under APHIS–PPQ regulations. Currently, under 7 CFR part 340, any product containing a GE event that has been deregulated by APHIS may be imported into the United States without further regulation by APHIS, except those regulations that APHIS imposes on the non-engineered variety of that product, for example, phytosanitary considerations. The United States does not require any special permission to import crops produced overseas that have been deregulated by APHIS, nor is there a requirement to label or declare GE content for shipments containing only products deregulated within the United States.

Importation of any regulated articles into the United States requires an import permit or an import notification issued by APHIS. The majority of the import permits issued by APHIS over the past 19 years have been for small amounts of seeds, insects, or micro-organisms to be used for contained research. A list of these permits can be found on the BRS Web site http://www.aphis.usda.gov/brs/database.html. A separate release permit or release notification would be required for field testing any of these regulated articles.

If a foreign company or government wants to import a currently regulated GE plant into the United States without APHIS' regulatory oversight, it must first submit a petition to APHIS through a domestic agent requesting deregulated status for that product. The plant is subjected to the same case-by-case assessment required for domestic products. If APHIS determines that the plant poses no more of a plant pest risk than the same plant without GE traits, APHIS may grant the GE plant nonregulated status, and the plant, its progeny, and products derived from the plant can be imported into the United States subject only to phytosanitary or other requirements imposed on the non-engineered varieties of that species, and any requirements imposed by other U.S. regulatory agencies such as FDA or EPA.

Currently, APHIS regulations do not distinguish between requests for deregulation of imported GE products intended for large-scale environmental release (commercial production) in the United States and GE products imported only for non-propagative uses (food, feed, or processing, often abbreviated "FFP"), which the importer intends to deliberately release into the environment. In most cases, the developer of a new GE plant with commercial value will seek full deregulation in the United States, allowing use for food and feed, as well as for cultivation or propagation. However, situations may occur where the developer wishes to import a GE plant or a viable GE plant product only for food, feed, or processing with no intent to grow that plant in the United States. However, unintended release of the plant may result due to spillage, improper disposal, transportation accidents, theft, vandalism, undigested seed from food or feed use, or processing byproducts, and these releases could pose an unintended plant pest risk.

To date, APHIS has received only a small number of requests to import GE crops for FFP (such as processing of canola seed into oil), and these have been addressed on a case-by-case basis based on familiarity with the crop, the inserted gene or new trait, and the import conditions and intended use. In the past, APHIS has allowed importation of a product into the United States only for processing, following an assessment based on APHIS' familiarity with the crop and the trait. In the assessment, APHIS determined that the product was not considered to be a regulated article under the conditions proposed. In each case where an importation was authorized by APHIS, FDA had previously completed a consultation on the crop.

Rationale for Re-evaluation of APHIS Requirements for Importation of Non-propagative Regulated Articles

As part of the regulatory revision process, APHIS may need to address requirements for environmental risk assessment for products imported only for non-propagative use. Risk assessment is based on the concept that

risk = (hazard or *potential harm) X (exposure* or *frequency)*

and, therefore, GE FFPs can be presumed to pose less of a risk than the equivalent product intended for large scale planting due to a large reduction in the magnitude of environmental exposure. Reasons for APHIS to re-evaluate its requirements for imported, GE FFPs include:

- A recognition that GE crops intended for food, feed, or for processing will generally pose a substantially lower potential risk to the environment or to biodiversity than GE crops intended for environmental release.
- A decision that a full environmental risk assessment is not necessary to ensure environmental safety for products imported for non-propagative use could provide some regulatory relief for the regulated industry and make more efficient use of agency resources while continuing to ensure environmental protection.
- The United States currently exports large amounts of GE commodities, mostly corn and soybeans, that are intended only for use as food, feed, or for processing. The United States could provide an example for countries in the early stages of developing their own biosafety regimes if it implements a simplified, yet science-based, system for GE FFP imports.

Regulated Articles in Commodity Shipments

The first section of this discussion presents options for environmental risk assessment requirements with respect to decisions to import specific GE events or products for the purposes of food, feed, or processing only. However, there is also the broader question of how the United States, and, specifically, APHIS should address issues related to unintentional or unauthorized importation of GE products into the United States that have not completed APHIS regulatory review. This would include low level, unintended presence of regulated GE products, and could also include larger amounts of regulated products from exporters who are unfamiliar with, or do not comply with, U.S. domestic regulations.

Currently, the United States is a major exporter of bulk grain products, so the importation of GE varieties of these crops that are developed elsewhere is currently a minor concern. The United States does import large amounts of agricultural products such as canola, including GE canola, from Canada for processing into oil. APHIS works closely with Canada as new GE varieties are introduced to facilitate synchronous approvals when possible.

However, as noted above, GE products are in development in a number of countries and it is likely that within a few years these could end up in seed, commodity, or food shipments to the United States. As new GE products are developed (including grains, fruits, and vegetables) and commercialized overseas, the United States needs to consider development of mechanisms to ensure these products have undergone appropriate safety assessment before entering the U.S. food supply or environment.

Trade Considerations in the Rule Changes

APHIS works actively in international standards-setting organizations, including the North American Plant Protection Organization (NAPPO) and the International Plant Protection Convention (IPPC), to establish internationally shared, science-based standards. In addition, BRS helped establish a unified U.S. Government Web site that contains key information, such as safety assessments, on all products that have completed regulatory review in the United States. This site is linked to the Biosafety Clearinghouse that was established under the Biosafety Protocol to help facilitate transboundary movement of living biotechnology products. APHIS decision documents are accessible through these sites.

The United States supports the World Trade Organization (WTO) view that if regulations are set arbitrarily, they could be used as an excuse for protectionism. Under the WTO, the Technical Barriers to Trade Agreement (TBT) tries to ensure that regulations, standards, testing, and certification procedures do not create unnecessary obstacles. The TBT agreement recognizes countries' rights to adopt the standards they consider appropriate—for example, to ensure human, animal or plant life or health, for the protection of the environment, or to meet other consumer interests. Moreover, members are not prevented from taking measures necessary to ensure that their standards are met, and the agreement encourages countries to use international standards where these are appropriate, but it does not require them to change their levels of protection as a result.

The regulatory revisions under consideration by APHIS will be science based, consistent with international standards, and designed solely to protect the environment, including plant health and human health. The proposed alternatives are consistent with the TBT agreement and would not be technical barriers to trade.

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Appendix G. Socioeconomic and Sociocultural Effects

Introduction

Society's views and attitudes about biotechnology are shaped by many factors such as a person's moral principles or values, available scientific data, fears of the unknown, and so on. Society's views and attitudes increasingly influence the acceptance of biotechnology. It is not the purpose of this section to explore the sources of prevailing societal views and attitudes about biotechnology; rather, this section will focus on the key themes that have emerged. These themes include the potential benefits of biotechnology, the public's perception of risk, the choices people have regarding biotechnology, and the distribution of benefits and burdens or risks of biotechnology across society. Each theme is discussed below.

Potential Benefits of Biotechnology to Society

Experts agree that there may be numerous agriculture, human health, and environmental benefits of genetic engineering. Potential benefits include, but are not limited to increased crop production, crops that resist pests and diseases, decreased use of pesticides, crops that can tolerate long-term storage and resist adverse environmental conditions, diagnostic tools and vaccines that help control animal disease, increased nutritional value and improved digestibility of foods, new products for health and industrial uses, decreased presence of undesirable substances in foods (saturated fats, natural toxicants, antinutrients, and allergens), and new sources of renewable materials such as vaccines, drugs, and bioplastics (Devernoe, 2000; Vogt and Parish, 2001; WHO, 2004).

Public Perception of Risk

With biotechnology, as with many sophisticated technologies, the pace of scientific research may move faster than the public's ability to understand and accept products developed from that research. A survey conducted by agricultural scientists at the Virginia Cooperative Extension Service examined the sources of public concern regarding biotechnology. The study examined the issues raised by the public and discussed by the media and correlated the frequency with which each issue was cited by the public or the media. These agriculture- and food-related concerns, including the frequency with which they were cited by both the public and the media, are summarized below in table G–1.

Table G–1. Agriculture- and Food-related Concerns As Expressed By the Public and Appearing in the Media

Category of Concern	Frequency (%)	
	Public (opinion survey)	Media (keyword search)
Weediness of genetically engineered (GE) plants	50	43.7
Gene transfer to wild plant relatives	30	39.1
Invasion by GE plant to sensitive habitats	20	31.6
Value and nutrition of GE foods	75	54.1
Safety of GE food	66.7	65.8
Labeling of GE food	58.3	59.5
Consumer acceptance of GE food	33.4	44.2
Use of biotechnology products	73.3	56.7
Ethical, religious, and/or moral concerns	60.0	44.2
GE patents and freedom of information	46.6	49.3
Impact of GE products on farming	26.7	37.4
Public safety concerns	78.5	71.2
Public input concerns	64.3	63.1
Explanation and acceptance of risk	57.1	48.4
Impact of GE education	72.7	76.5
Role of television and press in GE education	63.6	63.1
Academic responsibility to public	26.3	42.9
Public safety in developing countries	55.5	57.6
GE product availability in international countries	44.4	46.5

Source: Hagendorn and Allender-Hagendorn, 1995.

In the above study, 60 to 70% frequency was identified as high frequency. For the public, high frequency concerns were the value and nutrition of GE foods; the safety of GE foods; use of biotechnology products; ethical, religious and/or moral concerns; public safety concerns; public input concerns; impact of biotechnology education; and the role of television and the press in biotechnology education.

However, biotechnology does not appear to be a major concern of American consumers when compared to other issues impacting the food supply (Alexander and Toner, 2004). In January 2004, a survey group was asked "What, if anything, are you concerned about when it comes to food safety?" Responses to this survey are in table H–2, below.

Table G–2. Public Concerns Regarding Food Safety.

Concern	Percent
Food handling/preparation	29
Disease/contamination	22
Packaging	10
"Mad cow" disease	9
Ingredients	9
Chemicals/pesticides	6
Biotechnology	1

Source: Alexander and Toner, 2004

Some social scientists have also proposed that one major factor in the difference between biotechnology research and public acceptance of biotechnology relates to changing social attitudes towards scientific advancements over time. They acknowledge that the underlying reasons for these changes in attitude are "vast and complex." However, according to one social science research source, public concerns regarding agricultural biotechnology can be generally categorized in three areas (Albrecht, 2004):

1. Concern that the release of GE organisms could potentially result in unforeseen permanent damage to the environment;
2. Concern that GE crops may become weedy and unable to be controlled in the environment; and
3. Concern that large farms that utilize biotechnology will have a competitive advantage over small farms, resulting in further loss of small farms in the United States.

Social scientists have also explored the link between the public's familiarity with biotechnology and public perception of the risks associated with this technology. This research indicates that the relationship between public support of biotechnology, in general, and an individual's knowledge of the scientific aspects of biotechnology is inconsistent (Chess, 1998). One such study concluded that "perceived risk did not decrease as perceived knowledge of the potential hazard increased" (Frewer et al., 1994). However, other studies concluded that there were links between acceptance of technology and knowledge about that technology (Zechendorf, 1994; Hallman et al., 2004). For example, a survey found that a majority of those surveyed would be likely to purchase foods which were protected from insect damage and required fewer pesticides due to biotechnology. Therefore, knowledge about GE crops and foods, especially knowledge relating to the benefits of the technology, can increase favorable attitudes and public support (Alexander and Toner, 2004). However, while Americans think the topic of GE foods is interesting and would like more information about the topic, especially in reference to human health, most Americans know very little about GE foods (Hallman et al., 2004).

Some studies suggest that the issue of biotechnology resembles other issues that have become stigmatized in the public's opinion (Slovic, 2000). These factors include:

- a technology that is perceived to have involuntary exposure;
- a technology that is perceived to have disproportionate effects on sub-populations;
- a technology that is perceived to have unbounded effects (i.e., the effects are not well understood or the magnitude is not known); and
- a perception that the technology has violated what is "right."

Stigmatization is, therefore, generally a result of perceptions rather than factual information, and stigma can be addressed through risk communication efforts that provide information to the public (Slovic, 2000).

Choice

A contributing factor in the gap between scientific thought and public acceptance of biotechnology is the perception by some members of the public that the adoption of biotechnology-derived products results in a lack of consumer choice. Specifically, some individuals believe that the use of biotechnology will preclude the availability of non-GE derived products in the marketplace. The issue of how to address the concern about lack of choice has been discussed and debated frequently for GE food products. Product labeling has been one option suggested to address this concern (Chess, 1998). Some parties argue that product labeling that discloses the existence of GE-derived materials in food is the best way to offer consumers a choice between GE and non-GE products. Others argue that product labeling can actually misinform the public (Teisl et al., 2003). For example, labeling may be interpreted as a warning when none is implied (Carter and Gruère, 2003). Labeling can also be misleading: a label on canned peaches stating "Contains No GMOs" implies that there are genetically engineered peaches, when, in truth, none exist, and the label also implies that cans without the label may have GE content.[4] In addition, the complexity and cost of separating products in the marketplace make this option very difficult (Heritage, 2005).

Distribution of Benefits and Burdens

Society's views and attitudes regarding GE products are partly shaped by people's perception of how the benefits and burdens that result from the use of the technology are distributed. However, the distribution of benefits and burdens of biotechnology is disputed. Some critics claim that biotechnology research has largely taken place in the private sector with proprietary technologies and an orientation to commercial agriculture and may, therefore, disproportionately benefit wealthy individuals and countries. Unless there are policies in place to ensure that small farmers have access to delivery systems, extension services, productive resources, markets, and infrastructure, larger farmers are likely to capture most of the benefits through early adoption of the technology, expanded production, and reduced unit costs (Persley, 2000). An FAO report,

[4] FDA's rules covering the misbranding of foods can be found at 21 CFR 101.18.

The State of Food and Agriculture 2003–2004, voices similar concerns, stating that there are no major public- or private-sector programs to apply biotechnology to the critical problems of the poor or to target crops and animals that they rely on (FAO, 2004).

However, the same report by FAO states that biotechnology is capable of benefiting small, resource-poor farmers. Some GE crops, especially insect-resistant cotton, are yielding significant economic gains for small farmers (FAO, 2004). While technologies that require a certain institutional and managerial environment to function properly may not be effective for poorer farmers, GE crops may be relatively easy for farmers to adopt because the technology is embodied in the seed—rendering it scale-neutral and easily transferable (FAO, 2004). FAO also reports that since the benefits of GE crops have been distributed widely among industry, farmers, and consumers, intellectual property protection does not necessarily lead to excessive industry profits, and the producers and consumers are reaping the largest share of the economic benefits of GE crops, not the companies that develop and market them (FAO, 2004).

APHIS has attempted to conduct its programs, policies, and activities in a manner that does not preclude individuals or populations from participating in making decisions regarding GE crops. As previously mentioned, two of APHIS' guiding principles that set program direction and provide the foundation for decisionmaking are: 1) transparency of the regulatory process and regulatory decisionmaking, and 2) communication, coordination, and collaboration with a full range of stakeholders. Throughout the current process to determine whether and how APHIS will revise its regulations, APHIS has attempted to ensure that individuals and groups are informed of and comment on their regulatory actions. Specific actions that APHIS has taken in order to educate and inform individuals and groups are outlined in the section titled, "Executive Order 12898—Environmental Justice in Minority Populations and Low-income Populations," under "Special Considerations," which follows.

Another topic about which some have raised concern is the benefits and/or burdens infants and children could experience as a result of the use of biotechnology. For example, public comments have raised concerns that infants and children may benefit and/or suffer disproportionately from the consumption of GE crops, particularly in regard to nutrition and allergenicity due to their developmental stage, greater metabolic activity levels, and behavior patterns (see "Potential Allergenicity of Newly-Expressed Proteins in Foods Derived from GE Plants," in chapter 4, section A). However, to APHIS' knowledge, no scientifically substantiated human nutritional or allergenicity concerns, including concerns for children, have been identified with any of the GE crops currently on the market.

Although some individuals may be concerned that scientists might unknowingly create food allergens through genetic engineering, researchers are also attempting to use the technology to eliminate or reduce allergens, such as those found in peanuts, wheat, and soy (Bren, 2003). For example, researchers have genetically engineered soy (Herman et al., 2003) and rice (Matsuda et al., 1993) to eliminate expression of common allergenic proteins. Soy allergies are particularly common in infants and young children, according to the National Institute of Allergy and Infectious Diseases, and it is difficult to avoid eating soy because of its wide use in many processed foods including infant formula, cereals, and salad dressings" (Bren, 2003).

Infants and children may also be more susceptible to nutritional imbalances than the adult population because of their developmental stage as well as the limited number of foods that they consume. Grains, fruits, and vegetables that contain more nutrients are being developed and, in some cases, nutrients are being added to foods in an attempt to help prevent diseases (Bren, 2003). While the objective is to make food more nutritious, some people are concerned that modifying foods could unintentionally decrease the nutritional value of food. For children, this risk could be magnified if the modified food was one on which children's diets depended (Donaldson and May, 1999). The FDA's Office of Nutritional Products, Labeling, and Dietary Supplements is responsible for the development of policy and regulations regarding food nutrition and standards (see http://www.cfsan.fda.gov/~dms/onplds.html). For a discussion on analyzing the nutritional quality of GE plants, see section titled, "Composition of Foods from Genetically Engineered Plants Compared to Their Traditional Counterparts" (see chapter 4, section A).

Special Environmental Considerations

The National Environmental Policy Act

In the planning and implementation of its programs and actions, APHIS complies with the National Environmental Policy Act of 1969 (NEPA) and the regulations promulgated by USDA, APHIS, and the Council on Environmental Quality (CEQ) under NEPA. Together these have the underlying objective of requiring Federal decisionmakers to comprehensively consider the environmental consequences of their actions before making any firm decisions. In addition, NEPA and associated regulations provide guidance in the procedures that must be followed, the analytical process itself, and the ways of obtaining public involvement.

NEPA requires Federal agencies to consider potential environmental consequences in their planning and decisionmaking processes, and it requires them to prepare detailed statements (environmental impact statements) for major Federal actions which significantly affect the quality of the human environment. These statements must consider the environmental impact of the proposed action, adverse effects which cannot be avoided should the proposal be implemented, alternatives to the proposed action, the relationship between local and short-term uses of the human environment, and the maintenance and enhancement of long-term productivity, and any irreversible and irretrievable commitments of resources necessary to implement the action. This DEIS is prepared specifically to meet the needs of NEPA, 42 United States Code (USC) 4321, et seq.

Executive Order 12898—Environmental Justice

Executive Order (EO) 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Population," requires each Federal agency to make achieving environmental justice part of its mission by identifying and addressing, as appropriate, disproportionately high and adverse human health or environmental effects of its programs, policies, and activities on minority populations and low-income populations in the United States and its territories and possessions. In addition, the EO requires Federal agencies to conduct their

programs, policies, and activities in a manner so as not to exclude persons and populations from participation in or benefiting from such programs.

Certain proposed program actions require APHIS to prepare an environmental document that, among other things, considers the potential that the action could cause disproportionately high and adverse human health or environmental impacts on minority or low-income populations. While the analysis of environmental justice is treated within the context of the NEPA process, disproportionate effects on minorities and the poor will be considered even when actions are categorically excluded under NEPA.

In an attempt to ensure that APHIS' actions will not exclude persons and populations from participating in or benefiting from the potential regulatory changes, APHIS has communicated with a wide range of individuals and organizations. APHIS has informed the public of the potential changes to their regulations via the *Federal Register* (FR) (69 FR 16181 and 69 FR 3271–3272) and its website (http://www.aphis.usda.gov/brs/index.html) which includes such links as "News and Hot Topics" (http://www.aphis.usda.gov/APHIS/new_info.html) complete with recent press releases, meetings, revised regulations, compliance and enforcement, FR notices, and free-of-charge stakeholder registration. APHIS has also a Web page entirely devoted to the NEPA process as it pertains to the proposed rulemaking (http://www.aphis.usda.gov/brs/eis/index.html). APHIS has sought public and stakeholder opinion throughout the decisionmaking process by soliciting public comments via the *Federal Register* (69 FR 16181 and 69 FR 3271–3272) and holding stakeholder meetings to enable interested parties and APHIS scientists and policymakers to hold discussions. In addition, while the exact location of a field test site is considered confidential business information, in the interests of disclosure, concerned individuals and groups may obtain the State and county where field test sites are located.

In APHIS' opinion, agency oversight of regulated articles under 7 CFR part 340 does not currently have any disproportionate impacts on either minority or low-income populations, and APHIS does not anticipate any change in impacts on these populations should the Preferred Alternative be adopted. APHIS will continue to publicly announce potential modifications to policy, update its Web site with current information, and provide the public and stakeholders with opportunities to voice their opinion and potentially influence the decisions made.

EO 13045—Protection of Children From Environmental Health Risks and Safety Risks

EO 13045, "Protection of Children From Environmental Health Risks and Safety Factors," acknowledges that children may suffer disproportionately from environmental health and safety risks because of their developmental stage, greater metabolic activity levels, and behavior patterns, as compared to adults. This EO requires each Federal agency (to the extent permitted by law and when appropriate and consistent with the agency's mission) to identify, assess, and address environmental health risks and safety risks that may disproportionately affect children. Certain proposed program actions require APHIS to prepare an environmental document that, among other things, considers the potential for the action to cause disproportionately high and

adverse health and safety impacts on children. While the protection of children must be considered within the context of the NEPA process, disproportionate effects on children must be considered even in actions that are categorically excluded under NEPA. In APHIS' opinion, agency oversight of regulated articles under 7 CFR part 340 does not currently have any disproportionate impacts on children, and APHIS does not anticipate any change in impacts on this population should the Preferred Alternative be adopted.

EO 12114—Environmental Effects Abroad of Major Actions

Executive Order (EO) 12114, "Environmental Effects Abroad of Major Federal Actions," was written to require Federal officials to become informed of pertinent environmental considerations and take them into account, along with other national policy considerations, when making decisions on certain kinds of Federal actions (generally those that would have significant effects outside the jurisdiction of the United States). The EO specifically covers major Federal actions that significantly affect: (1) the global commons (environment outside the jurisdiction of any nation), (2) the environment of nations not participating in or involved in that action, (3) the environment of a foreign nation by providing to that nation a product that is toxic or radioactive and prohibited or regulated in the United States, and (4) natural or ecological resources of global importance designated by the President.

If the proposed action could potentially have significant affects on the "the global commons" and "the environment of nations not participating in or involved in that action," EO 12114 stipulates that the preparation of an EIS is appropriate.

As previously discussed in this document as issue 8 and in appendix H, APHIS recognizes that U.S. regulations on imported commodities have international implications. Many countries have implemented environmental regulations, and as indicated in the aforementioned sections, APHIS needs to consider how its regulatory changes might coordinate with existing international agreements related to agriculture, food, or trade, while providing leadership for countries in the early stages of developing their own regulations. APHIS is aware that this is a complex process and is committed to working with all outside parties to participate in developing an efficient regulatory process for agricultural biotechnology products as necessary.

Other Federal, State, and Local Statutes

APHIS must avoid "possible conflicts between the proposed action and the objectives of Federal, regional, State, and local (an in the case of a reservation, Indian tribe) land use plans, policies and controls for the area concerned" (40 CFR 1502.16(c)). In order to meet the terms of this requirement, APHIS complies with a number of other environmental acts, statutes, and regulations including the following Federal environmental acts: Plant Protection Act; the Federal Insecticide, Fungicide, and Rodenticide Act; the Toxic Substances Control Act; the Comprehensive Environmental Response, the Compensation, and Liability Act of 1980; and the Food Quality Protection Act.

In addition to APHIS, two other Federal agencies have a major responsibility in the oversight of biotechnology, FDA and EPA. While FDA is responsible for ensuring the safety of GE food and products for human and animal consumption, EPA is responsible for ensuring that pesticides, including those produced in living plants, are safe for human health and the environment. Through continuing interagency communication, APHIS remains informed of and involved in the development of EPA and FDA regulations and policies regarding biotechnology. APHIS is committed to the goals of the Framework for Regulation of Biotechnology as set out by the President's Office of Science and Technology Policy, and APHIS operates its biotechnology regulatory program in an integrated and coordinated fashion with FDA and EPA to minimize any potential environmental effects.

The States have implemented various environmental statutes and regulations (see table H–3). Many of the regulations and regulatory organizations that enforce them are direct parallels of the Federal regulations and regulatory organizations. However, there has been a diverse range of regulatory responses by States on GE crops and food. A report published by the Pew Initiative on Food and Biotechnology in December, 2004, recognized that the States have long shared responsibility with the Federal government for the enforcement of laws regulating pesticides and plant pests, some of which also cover GE crops. In addition to participating in the review of notifications and permits for GE crops, States have a particular interest in APHIS' oversight of field trials to ensure that experimental GE crops do not accidentally commingle with crops headed for the food supply (Taylor et al., 2004).

It is not anticipated that any State regulations regarding GE crops or food would conflict with any of APHIS' proposed regulation changes. APHIS will work closely with States to be sure that they are aware of field tests taking place within their jurisdiction to allow them to request any additional conditions.

Table G–3. Statutes Regarding Genetically Engineered Organisms

State	Has the State Enacted Legislation?	Description
Arizona	No	AZ does not have a statute regarding GEOs but does have a regulation that reinforces APHIS regulations for notifications and permits and allows for additional information to be obtained by the department to ensure proper confinement of the GEO. Genetically Engineered Organisms and Products (Ariz. Admin. Code Supp. § R3-4-901 (2004)).
California	No	--
Colorado	No	--
Hawaii	Genetically Modified Organisms (19 Haw. Rev. Stat. § 321-11.6 et seq. (2003))	Requires applicants to submit a copy of Federal notification or permit application to the state.
Illinois	Release of Genetically Modified Organisms Act (430 III, Comp. Stat. § 95/0.01 et seq. (2004))	Requires applicants to submit a copy of Federal notification or permit applications to the state and county official where release will occur, including a summary of CBI-redacted information. The state may seek public input or expertise in its review of a Federal permit or notification.
Iowa	No	--
Kansas	No	--
Maine	Genetically Engineered Plants and Seeds (7 Me. Rev. Stat. Ann. § 1050 et seq. (2003) and The Labeling Foods Free of Genetic Engineering (7 Me. Rev. Stat. Ann. 530-A et seq. (2003))	Requires dealers or manufacturers of genetically engineered seed to keep a list of growers who purchase GE seed. Foods containing 1% or less of GE materials can be labeled GE-free.
Minnesota	Genetically Engineered Organisms Minn. Stat. (§ 18F.01 et seq. (2003)) and Experimental Genetically Engineered Pesticide Product Registration (Minn. Stat. § 18B.285 (2003))	Provides comprehensive authority to the state to issue permits and notifications for field testing of GE plants and the release of experimental pesticide producing GE plants. Provides for inspections, penalties for violations, and process to commercialize GE crops.
Montana	No	--
New York	No	--
North Carolina	No; a GEO-specific statute passed in 1989 was allowed to “sunset” in 1995	--
North Dakota	No	--
Oklahoma	Oklahoma Agriculture Biotechnology Act (2 Okla. Stat. § 11-35 et seq. (2004))	Provides comprehensive authority to regulate GE crops only if applicants are not regulated by a Federal agency
Oregon	No	--
Texas	No	--
Vermont	Pest Survey (6 Vt. Stat. Ann. § 1030 et seq. (2003)) and (6 V.S.A § 611 (c) et seq. (2004))	Requires applicants to obtain a state permit for sale, movement, or release of a GE plant determined to be a plant pest. Requires all GE seed to have labeling specifying the traits of the seed and safe handling instructions.

Source: Taylor, 2004.

Appendix H. References

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Appendix J: Index