Genetically Engineered Organisms as a Special Case 9

In requesting this assessment, Congress asked OTA to compare non-indigenous species (NIS) and genetically engineered organisms (GEOs; box 9-A)---specifically, whether and how pre-release evaluations can reduce the risks of unwanted introductions (41). The comparison makes sense because the central issues for NIS and GEOs are the same, namely, making decisions regarding intentional introductions, devising strategies to prevent unintentional introductions, and planning eradication and control programs should releases have unexpected harmful effects.

Moreover, according to OTA's definition of non-indigenous, all GEOs are non-indigenous. OTA has defined MS to include species beyond their natural ranges, domesticated and feral species, and non-naturally occurring hybrids (see ch. 2, box 2-A). Most species used in genetic engineering research today are domesticated species and fall within this definition. When domesticated species long cultivated in the United States are genetically engineered and then released, they become new varieties of these NIS. Just as the products of domestication are non-indigenous, regardless of origin, so too are the products of genetic engineering. Indigenous species that have been altered via genetic engineering and introduced into the environment become non-naturally occurring, and therefore non-indigenous, varieties.

The overlap between GEOs and NIS goes beyond such functional and definitional issues, however. Federal agencies apply many of the same laws to NIS and GEOs, and some of the same legislative gaps and ambiguities hold for both categories. Overlap also occurs in the risk assessment procedures used for

Box 9-A–What Do You Call an Organism With New Genes?

Terms Used by OTA

OTA uses the adjectives genetically engineered and transgenic to describe plants, animals, and microorganisms modified by the insertion of genes using genetic engineering techniques. GEO is used in this chapter as an abbreviation for "genetically engineered organism."

Genetic engineering refers to recently developed techniques through which genes can be isolated in a laboratory, manipulated, and then inserted stably into another organism. Gene insertion can be accomplished mechanically, chemically, or by using biological vectors such as bacteria or viruses. The bacterium Agrobacterium turnefaciens is commonly used to carry genes into plant cells.

A GEO potentially contains genetic material from three types of organisms. Genes from one or more donor organisms are isolated for insertion into a recipient organism. A biological vector maybe used to insert the genes. Genetic material in the resulting GEO thus includes all of the recipient's genes, the isolated donor genes, and sometimes genetic material from the vector as well.

Many of the organisms being genetically engineered today are domesticated species. Domestication occurs when organisms are selectively bred by humans for desired characteristics. The term "domesticated" often is used in discussions of genetic engineering to indicate how likely an organism is to establish a free-living population. However, this usage can be misleading since domesticated organisms vary greatly in this regard. Some, like corn *(Zea mays)*, are incapable of living beyond human cultivation, whereas others, such as goats *(Capra hircus)*, readily form free-living populations.

Related Terms

Genetically modified organisms have been deliberately modified by the introduction or manipulation of genetic material in their genomes. They include not only organisms modified by genetic engineering, but **also those** modified by other techniques such as traditional breeding, chemical mutagenesis, and manipulation of sets of chromosomes.

Biotechnology refers to the techniques, including both genetic engineering and traditional methods, used to make products and extract services from living organisms and their components.

SOURCES: Office of Science and Technology Policy, "Principles for Federal Oversight of Biotechnology: Planned introduction into the Environment of Organisms with Modified Hereditary Traits," 55 *Federal Register* **31118 (July 31, 1990); U.S. Congress, Office of Technology Assessment A New** *Technological Era for American Agriculture, OTA-F-474* **(Washington, DC: U.S. Government Printing Office, August 1992).**

the GEOs and NIS, although in the recent past methods have developed more rapidly for GEOs. This chapter takes a closer look at these two areas-regulation and risk assessment—related to Federal review of GEO releases. The analysis draws heavily on the previous assessment of Federal coverage for NIS (ch. 6) and of risks associated with introductions (chs. 2, 3, and 4). The chapter begins, however, with a brief discussion of why comparisons between GEOs and NIS are sometimes controversial.

SOURCES OF CONTROVERSY

Despite the overlap between GEOs and NIS, comparisons between the two can arouse strong objections, especially among those in the executive branch charged with reviewing environmental releases of GEOs (20). Such reactions have origins in the technical and policy issues discussed below. They are complicated by the historical context—the rapid development over the past decade of Federal policies on GEOs (table 9-1) and the continuing dialogue among scientists, policymakers, and the public regarding the potential benefits and risks of GEO releases.

Table 9-1—Federal Policies and Regulations Related to the Environmental Release of GEOs Since 1984

Office of Science and Technology Policy	
1992	**Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment, 57Federal** *Register* **(FR) 6753 (Policy statement,)**
1990	**Principles for Federal Oversight of Biotechnology: Planned Introduction into the Environment of Organisms with Modified Hereditary Traits, 55 FR 31118** *(Proposed Policy)*
1986	**Coordinated Framework for Regulation of Biotechnology, 51 FR 23302 (Policy Statementar?d Request for Public** *Comment)*
1985	**Coordinated Framework for the Regulation of Biotechnology; Establishment of the Biotechnology Science Coordinating Committee, 50 FR 47174**
1984	**Proposal for a Coordinated Framework for Regulation of Biotechnology, 49 FR 50856** *(Proposed Policy)*
The President's Council on Competitiveness	
1991	**Report on National Biotechnology Policy** *(Policy Statement and Recommendations for Impementation)*
U.S. Department of Agriculture, Animal and Plant Health Inspection Service	
1993	**Genetically Engineered Organisms and Products; Notification Procedures for the introduction of Certain Regulated Articles; and Petition for Nonregulated Status, 58 FR 17044 (Final** *Rule)*
1992	**Genetically Engineered Organisms and Products; Notification Procedures for the introduction of Certain Regulated Articles; and Petition for Nonregulated Status, 57 FR 53036** *(Proposed Rule)*
1987	**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, 7 CFR 340** *(Final Rule)*
1986	**Final Policy Statement for Research and Regulation of Biotechnology Processes and Products. 51 FR 23336** *(Final* ***Policy*** *Statement)*
1986	**Plant Pests: 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, 51 FR 23352** *(Proposed Rule and/Notice of Public Hearings)*
U.S. Department of Agriculture, Office of Agricultural Biotechnology	
1990	**Proposed USDA Guidelines for Research involving the Planned Introduction into the Environment of Organisms with Deliberately Modified Hereditary Traits, 56 FR 4134** *(Proposed Voluntary Guidelines)*
1986	**Advanced Notice of Proposed USDA Guidelines for Biotechnology Research, 51 FR 13367 (Notice for** *Public Comment)*
U.S. Environmental Protection Agency	
1993	**Microbial Pesticides; Experimental Use Permits and Notifications, 58 FR 5878** *(Proposed Ru/e)*
1989	Biotechnology: Request **for Comment on Regulatory Approach, 54 FR 7027 (Notice)**
1989	**Microbial Pesticides; Request for Comment on Regulatory Approach, 54 FR 7026** *(Notice)*
1986	**Statement of Policy: Microbial Products Subject to the Federal insecticide, Fungicide, and Rodenticide Act and the Toxic Substances Control Act (TSCA), 51 FR 23313 (Policy Statement)**
—	**EPA has not yet issued proposed or final rules for the regulation of genetically engineered microbes under TSCA.**

SOURCE: Office of Technology Assessment, 1993

Technical Sources

Considerable controversy surrounded the first releases of GEOs because of concerns over their potential effects and how they should be evaluated before their release. In the absence of experience with GEOs, some scientists argued that experience with ' 'exotic' (i.e., non-indigenous) species might help provide guidance (29,32). However, the comparison of GEOs to NIS itself provoked debate,

The approach was criticized because GEOs introduced to the same environment as the parent non-engineered organism differ by only a few genes. Effects of the gene changes in GEOs might be well characterized, allowing better prediction of how they affect the organism's ecology. In contrast, most NIS differ from indigenous organisms by many genes that generally are not well characterized. Further, some comparisons of GEOs to harmful NIS, such as *kudzu (Puerario lobala)* and the sea lamprey *(Petrornyzon marinus),* were alarmist, inappropriately suggesting that all GEOs are potentially like the worst NIS.

These limitations, however, do not address the basic similarity between the *process* of introducing a MS and the *process* of introducing a GEO. Both involve the release of a living organism potentially capable of reproduction, establishment, and ecological effects beyond the initial release site (36). The specific characteristics of the organism and the receiving environment will determine the consequences of either type of introduction (18,36,37), In this regard, experience with NIS has proven quite useful in defining the types of ecological questions that should be raised before releasing a GEO into the environment (box 9-B) (23,37).

Policy Sources

A recurring theme in policy discussions of GEOs has been whether effective regulation can be accomplished under existing Federal statutes or whether new legislation is needed (25,41,42). For the interim, at least, this issue has been tabled by the development of the "Coordinated Framework for the Regulation of Biotechnology" by the White House Office of Science and Technology Policy (OSTP).

OSTP has announced policies related to Federal regulation of biotechnology several times since 1984 (table 9-1). General goals of these policy statements include:

- coordinating and streamlining Federal regulation, in part by clarifying the roles of various agencies;
- giving guidance to Federal agencies in their regulatory approach and scope; and
- ensuring such regulation adequately balances protection of human health and the environment along with the national interest in fostering growth of the biotechnology industry.

An important early conclusion was that existing legislation was generally sufficient to cover planned releases of GEOs to the environment (25). The President's Council on Competitiveness strongly reiterated this position in 1991: "The Administration should oppose any efforts to create new or modify existing regulatory structures for biotechnology through legislation' (28). This policy reflected, in part, a desire to support commercial development of biotechnology by reducing the regulatory burden on the industry (28).

Although both proponents and critics of genetic engineering agree that Federal agencies exercise sufficient oversight of most current GEO releases, the adequacy of the Coordinated Framework may be challenged in the future. Certain GEO releases may not be adequately covered by Federal statutes. In some cases, the application of existing statutes to genetic engineering requires application of laws beyond their initial intent. The result has been confusing regulations based on convoluted interpretations of legal definitions.

It is important to note that the Coordinated Framework is an executive branch policy and has no explicit basis in Federal law. This imparts a sometimes counter-productive flexibility. For example, repeated changes since 1984 in how OSTP defined which GEOs should be regulated helped stymie efforts by the Environmental Protection Agency to issue regulations under the Toxic Substances Control Act (39).

The Federal agencies that review environmental releases of GEOs have been faced with the practical reality of regulating an activity where political pressures are strong to allow releases, technical information for decisionmaking is sometimes insufficient, and legislative authority imperfectly matches the problems at hand. The procedures currently in place reflect compromises hard won over the past decade. And for the present, at least, the system generally works. In this light, the reluctance of regulators to revisit debates of the past concerning the risks of GEO releases is understandable. It may, however, leave them unprepared for the future when technical advances, the application of genetic engineering to a wider array of organisms, and the move to

Box 9-B–The Risks of Genetically Engineered Organisms: Lessons from Non-Indigenous Species

Can the Species Become Established Outside of Human Cultivation?

The risks associated with a NIS depend in part on whether it can become free-living. Species requiring human cultivation (e.g., many agricultural crops) are unlikely to become pests or harm natural ecosystems. GEOs formed by the insertion of genes into cultivated species similarly pose little risk, unless the inserted genes affect the organism's reliance on human cultivation or cause it to unintentionally harm other organisms.

Greater risks are associated with introductions of NIS that do not require human cultivation. Some can establish free-living populations and cause environmental or economic harm. Certain significant pests of agriculture and natural areas are escaped crop and horticultural plants (e.g., crabgrass, Digitaria spp., and Japanese honeysuckle, Lonicere *japonica)* or livestock (e.g., feral goats (Capra hircus)). NIS directly introduced *to less* managed systems, such as rangelands and forests, can affect other species in these systems. Melaleuca *(Melaleuca quinquenervia),* a major cause of habitat degradation in the Florida Everglades wetland system, was initially introduced for water management. Grass carp (Ctenopharyngodon idella), widely introduced for aquatic weed control, also increase water turbidity and destroy habitats of young fish. Thus, GEOs resulting from insertion of genes into potentially free-living species similarly are of greater concern because they might affect natural areas.

Can Genes Spread Through Hybridization?

A potential risk factor common to NIS and GEOs is that of gene spread to other species through hybridization (interbreeding). Genes can move from some cultivated crops that otherwise pose low risk. Notable examples include hybridization between rapeseed (Brassica napus) and wild mustards *(B. kaber, B. juncea, B.* nigra); cultivated and free-living squash *(Cucurbita pepo);* and between domesticated tomatoes *(Lycopersicon esculentum)* and wild tomato *(Lycopersicon pimpinnellifolium)* in South America. Hybridization between crop and weed species has sometimes given rise to new weeds like the Bolivian weed potato *(Solanum sucrense).* Moreover, the potential for hybridization between cultivated and wild and weedy relatives varies greatly among species. For example, although there is no evidence that genes move from carrots *(Daucus carota sativa)* to wild relatives like **Queen Anne's** lace *(Daucus* **carota)** in North America, gene exchange between alfalfa *(Medicago sativa)* planted for forage and wild relatives appears to be widespread.

The opportunity for hybridization also varies geographically. Most major agricultural crops lack free-living relatives (and therefore the opportunity for hybridization) in the United States because they originated in other areas of the world. Some exceptions are sorghum (Sorghum *bicolor),* sunflower *(Helianthus* spp.), clover *(Trifolium* **spp.), and tobacco** *(Nicotiana tabacum).* Wild cotton *(Gossypium tomentosum),* which potentially might hybridize with genetically engineered cotton, exists in Hawaii, but not elsewhere in the United States.

The potential for gene spread from GEOs to other species is thus an important consideration in risk assessments. All else being equal, GEOs lacking free-living relatives in the area of release pose fewer risks. The consequences of gene movement from GEOs to other species depend on what traits they confer. Some, like genes affecting fruit color, pose little risk. Greater concerns center on genes that might transfer harmful traits to free-living species. For example, much current research involves insertion of genes for herbicide resistance into crop plants to allow control of weeds without harm to the crop. Should this trait be transferred to weedy relatives, the usefulness of a particular herbicide for weed control could be lost.

SOURCES: N.C. Ellstrand and C.A. Hoffman, "Hybridization as an Avenue of Escape for Engineered Genes," *BioScience,* vol. 40, No. 6, pp. 438-442, June 1990; R.S. Grossman, "Biotechnology Products in the Field: Bringing Regulation Closer to Home," American *Journal of Public Health*, vol. 82, No. 8, August 1992, pp. 1165-1 166; K.H. Keeler and C.E. Turner, "Management of Transgenic Plants in the Environment," *Risk Assessment in Genetic Engineering,* M.A. Levin and H.S. Strauss (eds.) (New York, NY: McGraw-Hill, Inc., 1980); E. Small, "Hybridization in the Domesticated-Weed-Wild Complex," *Plant Biosystematics,* W.F. Grant (cd,) (New York, NY: Academic Press, 1984), pp. 195-210; H.D. Wilson, "Gene Flow in Squash Species," Bioscience, vol. 40, No. 6, June 1990, pp. 449-455.

Table 9-2—Who Regulates Which GEO Releases?

Agency	Regulated category	Authority[a]	Types of approved releases thus far	Number
APHIS	Plant pests	Federal Plant Pest Act Plant Quarantine Act Federal Noxious Weed Act	Transgenic plants	327 contained field tests at 660 sites in 37 States and Puerto Rico[b]
	Veterinary biologics	Virus-Serum Toxin Act	Live animal vaccines (microbes)	25 controlled releases; 7 licenses for commercial distribution[c]
EPA	Pesticides	Federal Insecticide, Fungicide and Rodenticide Act	Pesticidal microbes	42 small-scale field tests[d]
			Pesticidal plants	3 releases of over 10 acres[e]
	Other microbes	Toxic Substances Control Act	Microbes modified for Improved detection or enhanced nitrogen fixation	19 small-scale field releases[f]

a For full citations of Federal laws see text.
b As of October 1992. The "Flavr Savr" tomato was recently exempted from regulation, permitting requirements were relaxed in 1993 for 5 categories of GEOs, to allow notification of APHIS rather than requirement of a permit before release.
c Number permitted during fiscal years 1989 through 1992.
d As of July 1993, covering the period 19S4 through 1993.
e Experimental Use permits were issued fo, large-scale tests of *Bacillus thuringiensis* delta endotoxin produced in cotton, corn, and Potato. As of July 1993.
f As of Feb. 3, 1993,

SOURCES: F. Betz, Environmental Fate and Effects Division, EPA, FAX to E.A. Chornesky, Office of Technology Assessment, Aug. 2, 1993; D.E. Giamporcaro, Section Chief, TSCA Biotechnology Program, letter to P.N. Windle, OTA, Apr. 29, 1993; J.H. Payne, Associate Director Biotechnology, Biologics, and Environmental Protection, APHIS, letter to P.N. Windle, Office of Technology Assessment, Nov. 10, 1992; B. Slutsky, "Pesticidal Transgenic Plants: Risk Issues," *Pesticidal Transgenic Plants: Product Development, Risk Assessment, and Data Needs* (U.S. EPA Conference Proceedings: Nov. 6 and 7, 1990), pp. 127-132.

commercialization of GEOs broaden the scope of regulatory issues.

FEDERAL REGULATION OF GEO RELEASES

Under the Coordinated Framework, two Federal agencies, the U.S. Department of Agriculture's Animal and Plant Health Inspection Service (APHIS) and the U.S. Environmental Protection Agency (EPA) oversee most environmental releases of GEOs (table 9-2).

APHIS regulates releases of GEOs for which the donor, recipient, or vector of new genetic material is a potential or actual plant pest (box 9-C). In the past, anyone wishing to move or release such organisms needed to apply for a permit certifying the action did not pose a significant risk to agriculture or the environment. APHIS then evaluated the ecological risks of release by conducting an in-house environmental assessment for each permit granted. APHIS recently relaxed these permitting requirements for transgenic potatoes *(Solanum tuberosum)*, tomatoes *(Lycopersicon esculentum)*, cotton (*Gossypium hirsutum*), soybean *(Glycine max)*, tobacco *(Nicotiana tabacum)*, and corn *(Zea mays)* that fulfilled certain eligibility criteria and released according to specified performance standards,[1] These cases now require only that APHIS be notified in advance of field trials. In practice, APHIS has overseen releases of a wide array of genetically engineered plants because the bacterial vector used to insert genes is itself a plant

[1] 58 *Federal Register 17044* (March 31, 1993)

Box 9-C-Which Categories of GEOS APHIS Regulates as "Plant Pests"[1]

Definition of a Regulated Article

"Any organism that has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in 340.2 of this part and meets the definition of a plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the Deputy Administrator determines is a plant pest or has reason to believe is a plant pest. Excluded are recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only non-coding regulatory regions."

Taxa Listed in 340.2

Viruses (all members of groups containing plant viruses, and all other plant and insect viruses); Bacteria(13 genera; gram-negative phloem-limited bacteria associated with plant diseases; gram-negative xylem-limited bacteria associated with plant diseases; all other bacteria associated with plant or insect diseases);

Other disease-causing organisms (all rickettsial-like organisms associated with insect-diseases; members of the genus *Spiroplasma;* mycopiasma-like organisms associated with plant diseases; mycopiasma-like organisms associated with insect diseases);

Algae (three genera of green algae);

Fungi (3 classes; 16 orders; 33 families; and ail other fungi associated with plant or insect diseases);

Plants (parasitic species in ***13*** families and 27 genera);

Animals (nematodes-20 families; snails-6 superfamilies and 1 subfamily; spiders, mites, and ticks—13 superfamilies; millipedes—1 order; insects-4 orders, 8 superfamilies, 53 families, 5 subfamilies, 3 genera)

Definition of a 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."

[1] APHIS has exempted from permitting requirements interstate movement of certain GEOs containing less than the complete genome of a plant pest and field releases of a set of tomatoes having altered softening properties. The agency recently relaxed the permitting requirements for several other categories of GEOs.

SOURCES: 7 CFR 340 (June 16, 1987) as amended, "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;" J.H. Payne, Associate Director, Biotechnology, Biologics, and Environmental Protection, APHIS, letter to P.N. Windle, Office of Technology Assessment, Nov. 10, 1992; U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Genetically Engineered Organisms and Products; Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status," proposed rule, 57 *Federal Register* 53036 (Nov. 6, 1992).

pathogen or because plant pathogen genes have been inserted to promote expression of other inserted genes,

Uncontained uses of live animal vaccines (veterinary biologics) are also regulated by APHIS. A permit is required for experimental use of a vaccine, and vaccines must fulfill standards of product purity, efficacy, and safety (to the environment, human health, and animal health) before licensing and wider distribution. APHIS has not issued specific regulations for GEOs in this category, but has instead relied on existing regulations for live vaccines.

EPA regulates releases of genetically engineered microbes under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[2] and the Toxic Substances Control Act (TSCA).[3] Final regulations have not yet been promulgated under either Act for small-scale releases; consequently, the agency is operating under interim policy. The GEOs regulated under FIFRA are pesticide-producing microbes. Users must notice EPA before small-scale field tests. Following notification, the agency may require submission of materials for an Experimental Use Permit before release. EPA also intends to regulate under FIFRA the commercial distribution and sale of transgenic plants engineered for pest and disease resistance (i.e., because of the pesticidal substances they produce) (34). This category eventually is likely to include agricultural crops, ornamental plants, aquatic plants, and species for forest and rangeland management (48).

Under TSCA, EPA regulates transgenic microbes not covered by any other statute, for example, nitrogen-fining bacteria or microbes used for environmental remediation. This regulation rests on extension of TSCA's definition of ''chemical substance' to live organisms-an interpretation that has been a source of continuing debate and could be subject to legal challenge in the future. Transgenic microbes constructed by transferring genes between genera or higher taxonomic categories are considered ''new chemical substances' under the agency's current policy (unless they are on the TSCA inventory). Notification of EPA is voluntary before experimental releases, but required before full general commercial use (6).

The National Institutes of Health (NIH) historically has had a role in evaluating environmental releases through its Recombinant DNA Advisory Committee. However, this committee has not reviewed any deliberate releases of GEOs since 1987 and voted in May 1991 to terminate over-

TIM McCABE

Several corporations hope to genetically engineer insect viruses-such as the celery looper virus that infects cabbage loopers (Trichoplusia ni) *and several other insect pests-into more potent insecticides.*

view in this area that overlaps with APHIS and EPA. The issue is now under consideration by the director of NIH (43).

Holes in the Coordinated Framework

Finding:

Some of the same gaps in current Federal authority and regulation that exist for NIS also apply to GEOs under the Coordinated Framework. In the foreseeable future, commercial development is likely to proceed for several categories of GEOs that lack Federal or State regulation of experimental release or commercial distribution. Similar gaps for NIS continue to allow some ill-advised introductions resulting in economic costs or environmental harm.

Because environmental releases of GEOs currently are regulated under many of the same statutes that cover NIS, several gaps in Federal coverage identified by OTA for MS also apply to GEOs. Most of the gaps raise few "real-world" concerns at present: environmental releases of GEOs through October 1992 primarily have been

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2 Federal Insecticide, Fungicide, and Rodenticide Act (1947), as amended (7 U.S.C.A. 135 et *seq.*).

3 Toxic Substances Control Act (1976), as amended (15 U. S.C.A. 2601 *et seq.).*

of only a few types of organisms (table 9-3). These generally have presented relatively low risks and are clearly covered by current Federal oversight. However, the gaps may become increasingly important as the range of biological origins and applications of GEOs expands over the next 5 to 10 years. This is especially worrisome given the rapid advances in genetic engineering technologies and the growing numbers of field releases. Between 1987 and 1991 alone, applications to APHIS for field testing of transgenic plants increased more than six-fold (49).

Some observers anticipate that Federal oversight under the Coordinated Framework will evolve to fill these gaps as needs arise (6,43). Experience with NIS has shown, in contrast, that under the constraints of budgetary limitations, Federal agencies sometimes hesitate to expand their regulatory domains, even where clear needs and authority exist (see boxes 3-A, 4-B). Moreover, statutory authority does not exist to fill certain of these gaps. Voluntary compliance by GEO producers—motivated by a desire to quell public concerns—also might help limit future problems resulting from regulatory gaps. One Limitation may be that, as the number of releases grows ever larger, public scrutiny of individual releases is likely to decline, potentially decreasing the incentives for producers to seek voluntary approval.

The following sections describe some areas where Federal authority to review GEO releases is lacking or ambiguous. This is not to say that every release of a GEO in these categories necessarily poses a risk. But these are areas where there is no experience on which to evaluate riskiness nor mechanisms yet in place to gain such experience. Moreover, the track record of harmful introductions of NIS in these same categories suggests a need for some level of review before GEO releases (chs. 2 and 4). These potential limits to the Coordinated Framework were addressed by Congress during consideration of the Omnibus Biotechnology Act of 1990 (40). The bill, however, was not enacted.

Table 9-3—Current and Potential Future Releases of GEOs

GEOs Already Released In Field Experiments
Microbes:
pesticidal microbes
nitrogen-fixing microbes
marker microbes for tracking environmental dispersal
live animal vaccines
Plants:
agricultural crops (e.g., tomato *(Lycopersicon esculentum)*, cotton (Gossypium *hirsuturn)*, corn *(Zea mays)*)
agricultural crops producing pharmaceuticals or specialty chemicals
forage crops (e.g., alfalfa *(Medlcago sativa)*)
trees (e.g., poplar *(Populus* spp.), walnut *(Juglans* spp.))
Geos *Currently Under Research for Future Releases*
Microbes:
microbes that break down chemicals for bioremediation
Plants:
ornamental plants
plants for range management
trees for timber production
trees for urban plantings
erosion control plants
Fishes:
game fish for fisheries management
fish for aquiculture (rapid growth, disease resistance, cold tolerance)
Invertebrate animals:
shellfish for aquaculture
crustaceans for aquaculture
nematodes (roundworms) for biological control
insects and arachnids for biological control

SOURCES: M. Fischetti, "A Feast of Gene-Splicing Down on the Fish Farm," *Science*, vol. 253, No. 5019, Aug. 2, 1991, pp. 512-513; P.K. Gupta et al., "Forestry in the 21st Century," *Bio/Technology*, vol. 11, No. 4., pp. 454-463, April 1993; E.M. Hallerman et al., "Gene Transfer in Fish, " *Advances in fisheries Technology and Biotechnology for Increased Profitability*, M.N. Voight and J.R. Bottia (eds.) (Lancaster, PA: Technomic Publishing Co., 1990), pp. 35-49; L.F. Elliot and R.E. Wildung, "What Biotechnology Means for Soil and Water Conservation," *Journal of Soil and Water Conservation*, vol. 47, No. 1, January-February 1992, pp. 17-20.

FISH AND WILDLIFE

No law directly provides for Federal oversight of interstate transport or release of genetically engineered fish (finfish and shellfish) or wildlife. Under the Lacey Act, controls over environmental releases of fish and game are State functions, although the U.S. Fish and Wildlife

Service (FWS) can play a role in limiting the interstate transport of species listed by States as prohibited or injurious (chs. 6, 7). Few States compensate for this lack of a Federal presence with comprehensive laws covering release of GEOs. Moreover, States have been discouraged from developing such laws by those concerned that States might obstruct the testing and development of agricultural GEOs like transgenic crops (9).

Future implementation of the Non-Indigenous Aquatic Nuisance Prevention and Control Act of 199@ could narrow this gap slightly by restricting the unintentional importation or transport of harmful aquatic GEOs. However, the Federal interagency task force implementing the Act has not yet addressed GEOs in any context.

Other significant areas remain uncovered by Federal law. No Federal authority exists to directly limit the interstate transport or release of aquiculture species, although this is an active area of genetic engineering research (19). Similarly, should genetic engineering techniques be applied to game species of fish and wildlife, there presently are no Federal requirements for review before release. Moreover, the agencies most likely to be involved, FWS and the National Oceanic and Atmospheric Administration, lack applicable policies on GEOs.

Some experts estimate genetically engineered fish will enter commercial distribution within this decade (1 1). Two have already been field tested in holding ponds. This category raises particular concerns because many fish can establish free-living populations.

U.S. FISH AND WILDLIFE SERVICE

A genetically engineered variety of striped bass (Morone saxatilis) *is likely to be among the first transgenic fish released.*

CERTAIN PLANTS

APHIS's current regulations for GEOs do not explicitly include large categories of plants (box 9-C). Listed as regulated are parasitic plants in 13 families and 27 genera that fulfill the definition of plant pest. Not included are numerous taxa containing species that are weeds or can become weeds in some habitats. Examples of the latter are Bermuda grass *(Cynodon dactylon),* which is an important turf grass and forage plant but also one of the worst weeds in many parts of the United States (4), as well as many plants used in ornamental horticulture, such as purple loosestrife *(Lythrum salicaria).* Should genetic engineering be used to develop new varieties of species for range management or ornamental horticulture (21), it is unclear whether they would be reviewed before release under the category of organisms ''altered or produced through genetic engineering which the Deputy Administrator determines is a plant pest or has reason to believe is a plant pest. '

Many genetically engineered plants (including some forage and ornamental plants) presently fall under APHIS review because the plant pathogen *Agrobacterium tumefaciens was* used as a vector for gene insertion (boxes 9-A, 9-C). New mechanical and chemical techniques for inserting genes into plants do not involve plant pathogens. Consequently, some genetically engineered plants produced by such methods also will not fall squarely under APHIS's authority, Again, it is unclear how the agency will choose to deal with these GEOs.

4 Nonindigenous Aquatic Nuisance Prevention and Control Act of 1990, as amended (16 U.S.C.A. 4705 *et* seq., 18 U. S.C.A. 42).

Users are required to contact APHIS regarding planned releases of unregulated GEOs only if they have reason to believe the GEO poses a risk of being a plant pest (44). Given the historical complacency regarding introductions of non-indigenous plants, expecting users to rigorously evaluate the risks of transgenic plant introductions may be unrealistic.

CERTAIN INSECTS AND INVERTEBRATES USED FOR BIOLOGICAL CONTROL

In the future, should genetic engineering techniques be applied to insects, nematodes, or other invertebrates, environmental releases of some products might fall outside APHIS's purview. The key criterion defining APHIS's authority is whether an organism is a potential plant pest (box 9-C). Some insects and invertebrates used in biological control clearly fall outside this category since they injure neither plants nor plant products, for example. an insect that eats or parasitizes another insect that is itself a plant pest (40). Given that the agency's present coverage of this category is uneven (ch. 6), and its authority is ambiguous, it is unclear how APHIS would deal with GEOs in this category. The Environmental Protection Agency has exempted such non-microbial biological control agents from regulation under FIFRA.[5] The agency still could step in to assume this role (6), although it has not yet shown any interest in doing so.

RESEARCH

In general, research releases of GEOs are subject to the same restrictions as non-experimental releases. Further, research conducted or funded by Federal agencies is subject to the National Environmental Policy Act.[6] The U.S. Department of Agriculture's Office of Agricultural Biotechnology recently released proposed voluntary research guidelines that apply only to USDA funded research (47). The guidelines rely heavily on input from the Institutional Biosafety Committees that exist at many public and private sector institutions conducting genetic engineering research. The committees originated to ensure that researchers follow guidelines developed by NIH. Their main role has been in the review of contained laboratory research on GEOs. The committees are predominantly composed of members with expertise in genetic engineering (38); an important issue will be whether the committees expand their membership to include ecologists and others with technical backgrounds more appropriate for evaluating the safety of field releases.

Research releases falling within the gaps listed above (fish and wildlife, certain plants, biological control agents) and not funded by Federal dollars may not be covered by the current framework. For example, no Federal agency would review the research release of a genetically engineered fish where the research is privately funded. The Toxic Substances Control Act does not cover non-commercial and strictly academic research releases of non-pesticidal transgenic microbes (30). Concerns over research gaps are not purely hypothetical, as was demonstrated when a researcher at Auburn University moved to conduct experiments involving releases of transgenic carp *(Cyprinus carpio)* in ponds where there was a risk of fish escape (box 9-D).

COMMERCIAL DISTRIBUTION AND SALE

Certain laws, such as the Federal Seed Act;[7] Virus, Serum, and Toxin Act (VSTA);[8] and FIFRA, set standards for accurate labeling and assurance of product purity and efficacy for live organisms in commerce. The Federal Seed Act covers agricultural seed, VSTA covers live mi-

[5] 40 CFR 152.20(a) (May 4, 1988).

[6] National Environmental Policy Act of 1969, as amended (42 U. S.C.A. 4321 *et seq.*).

[7] Federal Seed Act (1939), as amended 7 U. S. CA. 1551 *et seq.*).

[8] Virus, Serum, and Toxin Act (19 13) (21 U. S.C.A. 151 *et seq.*).

Box 9-D-Transgenic Fish: Events Surrounding the Auburn Experiments

Considerable controversy erupted in 1989 when a researcher at Auburn University in Alabama moved to conduct experiments with transgenic fish in outdoor holding ponds where there was a risk of escape. After some initial confusion over the appropriate Federal forum for review of the proposal's safety, oversight fell to the Cooperative State Research Service of USDA, which partly funded the experiments. The agency's first Environmental Assessment and its associated finding of no significant environmental impact was met with strong criticism. This prompted the agency to conduct a second assessment with assistance from APHIS. While this assessment also found no significant impact, the finding was contingent on substantial modifications at the site to prevent fish escape. Modifications included construction of new ponds at a higher elevation and filtration of pond effluent, in addition to the existing preventative measures of an 8-foot fence and bird netting above the ponds. No Federal scrutiny necessarily would have occurred had this research been funded by the private sector. In this case, the researcher voluntarily sought Federal oversight even prior to receiving Federal funding.

SOURCES: U.S. Department of Agriculture, Office of the Secretary, "Environmental Assessment of Research on Transgenic Carp in Confined Outdoor Ponds," Nov. 15, 1990; J.L. Fox, Wish Drift Between Agencies' Guidelines," *Biotechnology,* vol. 7, September 19S9, p. SS5.

crobes in animal vaccines, and FIFRA regulates microbial pesticides and pesticidal transgenic plants. These laws aim to protect against product misrepresentation and the distribution and sale of contaminants. The lack of equivalent protection for other types of organisms in commerce may become important as the living products of genetic engineering move toward commercialization. Flower seeds, for example, are not covered by the Federal Seed Act. Nor do any Federal laws or regulations currently specify labeling requirements for grown plants or insects and other microorganisms used in biological control.

An additional role of commercial statutes is to regulate usages of potentially harmful products like pesticides-only allowing certain uses under specified conditions. As agricultural GEOs move toward commercial sale, they will not be subject to such regulation. Under the Federal Plant Pest Act[9] and the Plant Quarantine Act,[10] the mechanism APHIS uses to allow commercial sales of GEOs is to formally exempt them at this stage from regulation.[11] For certain GEOs it may be more appropriate to place constraints on commercial applications; for example, it might be prudent to limit planting of certain transgenic cottons in Hawaii where the potential for hybridization with free-living cotton *(Gossypium tomentosum)* exists.

GAP FILLING BY THE STATES

A perceived lack of adequate Federal regulation has been the driving force behind State efforts to develop laws on GEOs. As of February 1991, nine States had laws specifically dealing with the release of GEOs, and about 30 percent of the States were in the process of developing GEO release and product policies (3). A total of six States introduced, and three enacted, legislation related to the environmental release of GEOs in 1991 (15).

In at least some cases, State laws may cover all releases of GEOs. Under the North Carolina Genetically Engineered Organisms Act, for example, "A genetically engineered organism may not be released into the environment, or sold, offered for sale, or distributed for release into the environment unless a permit for its release has been issued pursuant to this article."[12] Thus,

9 Federal Plant Pest Act (1957), as amended (7 U. S.C.A. 147a *et* seq.).

10 Plant Quarantine Act (1912), as amended (7 U. S.C.A. 151 *et* seq.).

11 7 CFR 340 (June 16, 1987) as amended.

12 General Stat. of North Carolina, sec. 106-64.

releases of transgenic fish in the State of North Carolina currently would require a State, but no Federal, permit (33). North Carolina, however, is an exception among the States in this regard.

Similar to the patchwork of State fish and wildlife laws (ch. 7), current State laws on GEOs vary widely in scope and rigor (43). Such inconsistency could create burdensome requirements for researchers and industry (13). One representative of the seed industry clearly expressed some of the potential hazards of multiple States' regulation:

> Few engineered crop varieties or hybrids, if my, could bear the cost and time involved in multiple registrations in 50 individual States. Environmentally this approach would also fall short, as environmental problems, should they occur, can hardly be expected to respect State boundaries. Thus, a Federal lead in regulation of engineered crop plants is essential, but can only become a reality if the final system gains the confidence of the public and the States (35).

A SURPRISE CONSEQUENCE OF APPLYING THE SAME LEGAL AUTHORITY TO NIS AND GEOs

Applying the same laws to NIS and GEOs may have some unanticipated results. A case in point is APHIS's recent move to relax permitting requirements for releases of certain transgenic plants. APHIS's authority here derives from the Federal Plant Pest Act and the Plant Quarantine Act, both of which were designed to protect U.S. agriculture from pests. Historically, this is an area where Federal preemption of the States is common; for example, the Federal Government may impose quarantines unsupported by the States or, alternatively, it may allow for more liberal interstate transport of commodities that the States would prefer to curtail (ch. 7). In a recent rule, APHIS asserted its authority to exercise this preemptive power in the area of GEO releases;[13] that is, where the Federal Government has moved to allow a release, States cannot prevent the release from occurring.

Whether APHIS's position here would withstand a challenge in the courts is open to question (8). The issue may be largely theoretical, however: legal challenge is unlikely since most States lack the technical expertise to evaluate planned releases of GEOs and rely heavily on APHIS's judgment (17,33). Moreover, the new regulations provide for notifying the States before GEO releases. Nevertheless, the example demonstrates an important point. As long as the same sections of the same laws are used as authority for both NIS and GEOs, any amendments to these laws will need to anticipate how they will affect Federal actions regarding both categories of organisms. Moreover, legal precedents established for one category may eventually be applied to the other (7).

ECOLOGICAL RISK ASSESSMENT

Since the first environmental release of a GEO in 1986, Federal agencies have reviewed, authorized, or permitted several hundred additional releases of genetically engineered plants and microbes under final or interim rules. The general approach has been to treat each release as allowed only after case-by-case evaluation (i.e., on a' 'not sure" list; see ch. 4). Central to the evaluation process is some form of risk assessment. The potential for high profits combined with vocal public concern has driven the rapid development of risk assessment methods for GEOs and a growing scientific literature in this area (table 9-4).

As with NIS, assessments of GEO risk usually center on characteristics of the organism, the environment into which it will be released, and the likelihood the GEO or new genes will spread to other locales. Of particular concern has been characterization of the effects of the genetic modification, specifically its stability and whether

[13] ''Genetically Engineered Organisms and Products: Notification Procedures for the Introduction of Certain Regulated Articles; and Petition for Nonregulated Status,'' Final Rule, 58 *Federal Register 17044* (March 31, 1993).

Table 9-4—Selected Recent Discussions of the Environmental Effects of Releasing GEOs

L.R. Ginzburg (cd.), Assessing Ecological *Risks of Biotechnology* (Butterworth-Heinemann: Boston, 1991).
M. A. Levin and H.S. Strauss (eds.), *Risk Assessment in Genetic Engineering (New* York, NY: McGraw-Hill, Inc., 1990).
D.R. MacKenzie and S.C. Henry (eds.), *International Symposium on the Biosafety Results of Field Tests of Genetically Modified Plants and Microorganisms* (Agricultural Research Institute: Bethesda, MD, 1990).
H.A. Mooney et al. (eds.), Ecosystem *Experiments,* Published on behalf of the Scientific Committee on Problems of the Environment (SCOPE) of the International Council of scientific Unions (ICSU) (Chichester, England; New York, NY: John Wiley and Sons, 1991).
National Research Council, *Field Testing Genetically Modified Organisms: Framework for Decisions* (Washington, DC: National Academy Press, 1989).
J.M. Tiedje et al., "The Planned Introduction of Genetically Engineered Organisms: Ecological Considerations and Recommendations," Ecology, vol. 70, No. 2, 1989, pp. 298-315. (Report from the Ecological Society of America).
U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Workshop on Safeguards for Planned Introduction of Transgenic Potatoes," Conference Report, 1991.
U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Workshop on Safeguards for Planned Introduction of Transgenic Corn and Wheat," Conference Report, April 1992.
U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Workshop on Safeguards for Planned Introduction of Transgenic Oilseed Crucifiers," Conference Report, 1990.
U.S. Environmental Protection Agency, *Pesticidal Transgenic Plants; Product Developrnent, Risk Assessmerrt, and Data Needs* (U.S. EPA Conference Proceedings: Nov. 6 and 7, 1990).

SOURCE: Office of Technology Assessment, 1993.

inserted genes might confer unwanted characteristics on the GEO or other species to which they might spread. Factors affecting the GEO or gene spread include how likely the GEO is to establish a free-living population outside of human cultivation and the presence of free-living relatives that might hybridize with GEOs.

A far greater number of authorized releases has occurred for plants than for microbes. Although the same categories of risk apply to both, development of general risk assessment methods has been less tractable for microbes. The biology and ecology of microbes in nature is relatively poorly understood (16), and predicting environmental effect and dispersal potential is difficult (2). Microbes present special problems in evaluating the potential spread of genes since gene exchange in nature can occur not only between different species, but also between different genera (27). In addition, populations of microbes evolve rapidly, complicating predictions of the possible long-term effects of inserted genes.

Comparing the Current Level of Review for NIS and GEO Releases

Finding:

While some categories of GEOs actually pose lower risks than similar NIS, pre-release evaluations for certain GEOs have been more rigorous. This inconsistency reflects the chronic underestimation of risk for NIS introductions in the past. Some of the approaches being instituted for evaluating risks of GEOs might usefully be transferred to NIS.

Comparison of the current level of review by the Federal Government for various categories of MS and GEOs shows that greater scrutiny often is applied to GEOs, even though some may pose lower risks than NIS (table 9-5) (see ch. 4). For example, until 1993, APHIS conducted an environmental assessment for each permitted release of a genetically engineered plant, even for plants highly dependent on human cultivation and lacking free-living relatives in the United States. In contrast, non-indigenous plants are routinely introduced in the United States for applications in

Table 9-5—Federal Pre-Release Requirements for Small-Scale Releases of Certain Non-Indigenous Species (NIS) and GEOs

	NIS	GEOs
Crop and forage plants	**No systematic review**	**If within APHIS's definition of a "regulated article" (box 9-C):** **Most require application to APHIS for a permit; APHIS conducts an environmental assessment; EPA reviews APHiS's assessments for pesticidal plants** **For certain regulated articles: no permit is required, instead requires notification of APHIS at least 30 days before the day of release** **If not a regulated article: same as for NIS**
Live animal vaccines	**Requires application to APHIS for a permit; APHIS reviews application**	**Same as for NIS**
Pesticidal microbes	**Requires notification of EPA; EPA may require additional information or application for an Experimental Use Permit; EPA reviews submitted material** **For "plant pests": APHIS also reviews material before release**	**Same as for NiS**
Non-pest, non-pesticidal microbes (e.g., nitrogen-fixing bacteria)	**No systematic review**	**Voluntary notification of EPA; EPA may request additional information; EPA reviews submitted material**

SOURCE: Office of Technology Assessment, 1993.

soil conservation and wildlife forage with no systematic review of the potential environmental consequences of release-although such species may be chosen specifically for the ability to establish free-living populations (ch. 6). Similarly, EPA does a case-by-case review of certain releases of transgenic microbes, such as nitrogen-fixing bacteria, but releases of equivalent non-indigenous microbes are not subject to any Federal oversight. If more rigorous standards are applied to under-evaluated categories of NIS in the future, methods already developed for GEOs could provide a useful model.

Impending Scale-Up of Releases for Agricultural GEOs

Finding:

Experience with NIS overwhelmingly has shown that an organism's effects and ecological role can change when it is transferred to new environments. This suggests a need for caution in extrapolating from the results of small-scale field tests of GEOs to larger scale releases. Also GEOs that pose a low risk in the United States sometimes may pose a higher risk in other countries.

Most releases of GEOs in the United States thus far have been small field tests (table 9-2). The geographic area of release will inevitably increase for approved GEOs, particularly as they enter the phase of commercial production, distribution, and sale. This issue looms large especially for agricultural releases: estimates are that commercial distribution for some crops under development could occur as early as 1994 or 1995 (5). The impending scale-up raises several as yet unanswered questions, recently illustrated by the case of transgenic squash *(Cucurbita pepo)* (box 9-E).

Box 9-E-Controversy Erupts as Upjohn's Transgenic Squash ("ZW-20") Moves Towards Commercialization

The case of squash *(Cucurbita pepo)* genetically engineered for disease resistance illustrates several impending issues: the complexity of some of the decisions ahead; needs for better use of field tests to evaluate the risks of large-scale releases; and potential problems in applying domestic decisions internationality.

in September 1992, APHIS announced its intent to rule that a transgenic squash produced by the Upjohn Co.—ZW-20-is not a plant pest and therefore is not subject to further regulation by the agency. This variety contains genes from two plant virusesthat confer enhanced disease resistance. APHIS's ruling would be essential to the squash's commercial distribution. Calgene's Flavr Savr™ tomato (Lycopersicon esclentum)is the only other transgenic plant that the agency has ruled is not a plant pest.

Respnse to APHIS's plan, especially from environmental organizations, was strongly negative. Upjohn's petition was criticized for its scientific in accuracies and failure to cite important research. Further concerns were that APHIS apparently took the scientific content of Upjohn's petition at face value, and, in the absence of outside reaction, might have allowed commercialization of ZW-20 without additional analysis.

instead, however, APHIS issued a second call for public comment in March 1993. The agency specifically requested further information on the potential for hybrization between ZW-20 and free-living squash and whether transfer of disease resistance genes to free-living populations would affect their weediness. APHIS also contracted with Hugh Wilson, an expert on squash genetics at Texas A&M University, to prepare a report addressing these issues.

Wilson's report clearly identified several important risks. The potential for hybridization with ZW-20 would be great throughout the 12-State range of free-living squash. Moreover, free-living squash are already significant agricultural weeds in some areas and the transfer of new disease resistance genes to these populations could enhance their weediness. Gene transfer might also erode the genetic diversity of the free-living squash populations-a potential gene source for future squash breeding.

(continued)

WHAT IS THE ACCEPTABLE LEVEL OF RISK FOR GEO RELEASES?

Finding:

Proposals approved to date by APHIS for small-scale field releases of GEOs have been low risk. For the most part, APHIS has not yet been challenged to evaluate proposals posing intermediate risk levels. It is unclear how the agency plans to deal with this difficult task of setting acceptable levels of risk, especially as APHIS has not yet standardized its procedures for evaluating the risks associated with NIS.

Permit applications to date primarily have involved low-risk GEOs, such as those lacking free-living relatives in the United States, or involving genes that would pose negligible risk even if transferred to free-living relatives. Decisions concerning which releases to allow will become increasingly complex as the numbers and types of GEOs increase (table 9-3) and GEOs posing more intermediate levels of risk begin to be proposed for release.

APHIS is operating under statutes designed to protect U.S. agriculture from harmful pest species. Neither the Federal Plant Pest Act nor the Plant Quarantine Act contains any specification of what level of "harm" might be acceptable. This is in contrast to commercial statutes like FIFRA and TSCA, which give explicit instructions on how benefits should be weighed against risks. APHISs current regulations give no indication of how acceptable levels of risk are to be set.

Some perspective on how the agency balances such issues might be gleaned from its experience with NIS. Here APHIS weighs preventing entry of new plant pests against the economic desirability of free trade (see ch. 4). Critics complain the agency often errs in the wrong direction by

Although hybridization between free-living and domesticated squash has probably occurred throughout history, hybridization involving the transgenic squash poses special concerns. According to Wilson, the novel *source* of the disease resistance genes (viruses) "represents, within the biological and historical context . . . an unknown and untested factor. The process of injecting a foreign genetic element. . . that has no precedent within the phylogenetic history of a complex crop-weed system such as C. pepo, constitutes a biological risk." Further, the magnitude and impacts of this risk are "difficult-if not impossible-to predict."

APHIS's final ruling on ZW-20 is expected sometime during the fall of 1993. In the interim, Upjohn is conducting additional field tests to address many of the important issues. According to one USDA official, APHIS plans to make its decision regarding ZW-20 according to the same criteria used to judge varieties produced by traditional breeding. However, the consequences of gene transfer from domesticated to free-living plants have not been examined in the past. So, even traditional plant breeding provides little experience on which to base a regulatory decision.

If APHIS rules to allow commercialization of ZW-20, another issue will arise. Free-living squash also occur in Mexico and the export of ZW-20 seed to Mexico could pose additional potential risks.

SOURCES: R. Goldburg, Senior Scientist, Environmental Defense Fund, letter to Chief, Regulatory Analysis and Development, U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Oct. 19, 1992; J. Payne, Senior Microbiologist, Biotechnology, Biologics, and Environmental Protection, Animal and Plant Health Inspection Service, U.S. Department of Agriculture, personal communication to E.A. Chornesky, Office of Technology Assessment, July 13, 1993; J. Rissler et al., "National wildlife Federation Comments to USDA APHIS on a Proposed Interpretive Ruling Concerning Upjohn's Transgenic Squash," Oct. 19, 1992; U.S. Department of Agriculture, Animal and Plant Health inspection Service, "Notice of Proposed Interpretive Ruling in connection With the Upjohn Company Petition for Determination of Regulatory Status of ZW-20 Virus Resistant Squash," 57 *Federal Register* 40632-40633 (Sept. 4, 1992); U.S. Department of Agriculture, Animal and Plant Health Inspection Service, "Proposed Interpretive Ruling in Connection with the Upjohn Company PetitIon for Determination of Regulatory Status ZW-20 Virus Resistant Squashp" 5S *Federal Register* 15323 (March 22, 1993); H.D. Wilson. "Free-Living *Cucurbita pepo* in the United States: Viral Resistance, Gene Flow, and Risk Assessment" contractor report prepared for the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, May 27, 1993; H.D. Wilson, Professor, Department of Biology, Texas A&M University, personal communication to E.A. Chornesky, Office of Technology Assessment, July 16, 1993.

allowing new species and products to enter the country with few restrictions until risks are clearly demonstrated. Further, APHIS gives far greater attention to effects of its actions on agriculture, often neglecting effects on natural areas. This is of particular concern since upcoming GEO releases may have the potential to invade natural areas, or to affect populations of non-target species through their pesticidal properties.

RESULTS OF CONFINED FIELD TESTS AND POTENTIAL RISKS OF LARGER SCALE RELEASE

In approving the hundreds of test releases of transgenic plants thus far, APHIS has placed considerable emphasis on confinement—requiring that special precautions be incorporated into experimental protocols to prevent gene spread. Such precautions include destroying the plants before they flower or removing the flowers. Sometimes non-engineered plants are planted around the perimeter of an experiment to ''trap" pollen from the transgenic plants. Test fields also may be isolated a certain distance from other fields to minimize the chance of pollen transfer.

General agreement exists that confinement will become infeasible for many GEOs when they are released on a large-scale or go into commercial sale. The range of different environments into which a GEO is released will also increase. If changes in environment influence such risk factors as likelihood of establishment or dispersal, the relative risk of a release may increase with scale-up. Evidence from experiments with transgenic crucifers (plants in the mustard family) in England already has demonstrated variation among sites in the plants reproduction and other features that affect the potential for establishment (10).

Confined experimental releases conducted thus far demonstrate the characteristics, stability, and performance of GEOs—attributes important to evaluate during product development. They do not, however, necessarily provide any additional information on the ecological risks posed by a GEO under unconfined conditions or whether these risks will change as the scale of release increases (49). An analysis by the National Wildlife Federation showed that, for the 115 field releases permitted by APHIS from 1987 through 1990, the required final report was filed for only half (24). And most lack data on potential environmental effects that could be used for scale-up decisions. Nevertheless, proponents of genetic engineering have used the approval of, and low risk attributed to, small-scale experimental releases as evidence that permitting requirements for field tests are far too stringent (1).

In new regulations issued in 1993,[14] APHIS used the same reasoning to justify why certain releases of GEOs should require only agency notification rather than receipt of a permit. This probably poses few problems for the bulk of low-risk GEOs that will fall under the new regulations. It does, however, establish a poor precedent for higher risk GEOs. Especially for these, small field trials will need to better incorporate research and monitoring designed to evaluate the ecological risks of larger scale releases.

In the absence of such research, it is unclear what information will be used to make scale-up decisions. APHIS assumes that petitions to exempt an organism from regulation (i.e., allow commercial distribution) will include the necessary information to judge whether a GEO will cause significant environmental impacts when grown under unconfined conditions (26). However, the existing data applicable to such decisions are patchy at best.

Some groups in the private sector also have conducted or funded experiments to determine whether genes are likely to spread from transgenic crops by hybridization with wild and weedy

DAVID NANCE

The cotton boll at left (Gossypium hirsutum) *was protected from pests by a gene from Bt* (Bacillus thuringiensis). *Domesticated cotton has wild relatives (G.* tomentosum) *in Hawaii and elsewhere in the world that potentially could hybridize with the genetically engineered form.*

relatives (22,49). But, Federal investment in basic research in this area has not occurred in the United States until quite recently. The 1990 Farm Bill[15] required USDA to allocate 1 percent of its research budget to "biotechnology risk assessment research." The Cooperative State Research Service administers the program, which is expected to provide about $1 million annually in research grants (14).

HOW TO DEAL WITH INTERNATIONAL TRADE IN GEOs?

An even greater level of scale-up will occur when GEOs enter international commerce. Current Federal regulations do not address export of GEOs (44), although the risks associated with releases in other countries sometimes may be substantially greater than in the United States (box 9-B) (18, 23). Further, recipient countries for exports may themselves lack laws or regulations requiring oversight of GEO releases (12).

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14 58 *Federal Register* 17044 (March 31, 1993).

15 The Food, Agriculture, Conservation, and Trade Act of 1990, Public Law 101-624.

Most important crops lack wild and weedy relatives in the United States because they originated elsewhere, However, in countries closer to these crops' centers of origin, wild and weedy relatives generally are common. Close relatives of corn, tomatoes, and potatoes are common in Central and South America. In these areas the risk would be far higher that engineered genes might spread through hybridization *(45,46)*. Moreover, the small fields surrounded by vegetation typical of farming in developing countries provide greater opportunity for contact and hybridization with wild and weedy relatives (4).

A Question of Values: The Hazards of Our Successes

Objections to the first releases of GEOs commonly addressed the intrinsic merit of altering the natural world. This issue has been less prominent recently probably because it is less germane for agricultural releases to environments already highly modified by human manipulation. It may, however, reemerge as GEOs begin to be released into natural areas,

In many cases, NIS are valued by natural resource managers because of their ability to live in stressed, polluted, or otherwise degraded habitats where comparable indigenous species cannot dwell. Concerns have been voiced that genetic engineering may pose a similar opportunity to deal with environmental degradation not by fixing the problem but by changing the managed species.

> In the past, we tried to control pollution to accommodate plants and animals. Now, new [genetic engineering] techniques give us the power to control plants and animals to accommodate pollution. . . . In the past, petrochemical companies engineered pesticides to make them compatible with crops. Now they can engineer crops to make them compatible with pesticides (31).

The potentially vast opportunities genetic engineering brings also will pose certain implicit questions about the biological future of the country. As with NIS, managers of natural areas may need to decide between indigenous species and GEOs, or between improving habitats and stocking degraded habitats with GEOs that are more stress tolerant. As with NIS, explicit articulation of such choices and the development of clear policies is needed at a national level.

CHAPTER REVIEW

This chapter examined how the Federal Government oversees the environmental release of GEOs. Many low risk GEOs have been subject to a level of review never applied to potentially harmful NIS. However, other important issues—such as the need for better research on higher risk GEO releases and post-release monitoring-have received scant attention. The current Federal framework for regulating release of GEOs employs laws that were not designed for this purpose. As for NIS, a patched-together approach has resulted-one that leaves significant areas unaddressed and creates confusion for industry, academia, and government.

The kinds of GEOs discussed here seemed futuristic only a few years ago. In the next chapter, OTA takes a closer look at the future and the kinds of global changes that may further shape the impacts of harmful NIS.