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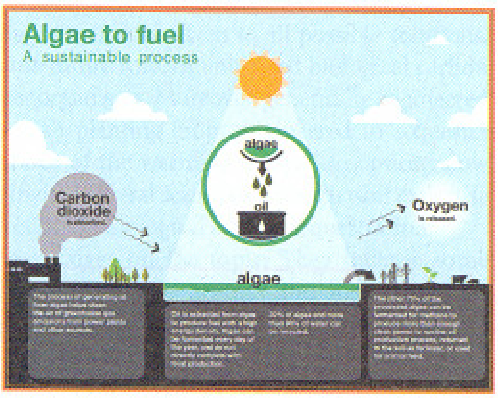
## NEWS AND OPINION



## OVERVIEW ARTICLES






*Cover: View of a clone bank of genetically engineered poplars incorporating approximately a thousand insertion events of various containment genes, which are intended to mitigate or prevent gene flow. The trees are being studied for development of the species as a biofuel feedstock; genetic engineering holds the promise of producing varieties that would have a range of advantageous properties. These trees are in principle ready for field evaluation through to flowering. Yet although the poplar genotypes used do not spread or mate with wild relatives in the region, current regulations require costly monitoring of the trees and their complete removal from the environment after study because of presumed hazard should transgenes disperse by pollen, seed, or vegetative establishment. In the article that begins on p. 729, Steven H. Strauss and his colleagues describe the far-reaching impact of regulations affecting the production of genetically engineered perennial biofuel crops and propose a regulatory scheme that would permit low-level presence of transgenes in nearby vegetation under certain conditions. The article is one of six included in* BioScience*'s Special Section on biological carbon sequestration. Photograph: Steven H. Strauss.*

# Far-reaching Deleterious Impacts of Regulations on Research and Environmental Studies of Recombinant DNA-modified Perennial Biofuel Crops in the United States

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*Regulatory restrictions have increased in recent years on organisms produced using recombinant DNA and asexual gene transfer, a process commonly called genetic engineering or genetic modification. Regulatory agencies have raised special concerns and required additional scrutiny for perennial grasses and woody plants of interest for biofuels; these plants have incomplete domestication, invasive capabilities, and the ability to mate with wild or feral relatives. Regulations on these plants require extremely stringent containment through all phases of research and development, regardless of the source of the gene, the novelty of the trait, or the plants' anticipated economic or environmental benefits. We discuss the extent to which these requirements conflict with the realities of practical crop breeding, and prevent meaningful agronomic and environmental studies, thus hampering—and in most cases, precluding—the use of recombinant DNA breeding methods for perennial crop improvement. We propose regulatory reforms to better balance benefit and risk and remove unnecessary barriers to agronomic evaluations and environmental studies.*

*Keywords: transgene, poplar, switchgrass, genetically engineered organisms, genetically modified organisms*

**Cellulosic bioenergy from perennial crops such as grasses** and trees, especially from areas where they are grown on former or marginal agricultural lands, is expected to provide substantial improvements over starch- and oil-based annual crop feedstocks with respect to the net greenhouse gas emissions and overall environmental impact (Sheehan 2009). This bioenergy is therefore considered a significant tool for meeting renewable energy needs over the next few decades, and is a major plank in the ambitious goals of the Energy Independence and Security Act of 2007, which mandates a major role for new ethanol feedstocks to supplement maize ethanol (CRS 2007, Sedjo and Sohngen 2009). Cellulosic biomass crops also continue to feature prominently in the Obama administration's renewable energy goals (CCC 2009).

There are a number of different types of perennial energy crops and energy products under consideration. The major crop types are native and exotic species of grasses and trees, each offering widely different advantages and disadvantages with respect to agronomic, economic, and environmental impacts. For example, grasses can be more readily managed than trees using conventional farm equipment, and may more efficiently retain nutrients in root systems under repeated harvests (Christian et al. 2008). However, they also present substantial additional costs because they require periodic harvests, bundling, and massive storage facilities to mitigate significant risks of biodegradation. In contrast, woody crops can be harvested year round and used directly in energy production.

For all crop types, intensive conventional breeding programs that typically include highly diverse sources of germplasm, inter- or intraspecies hybridization, clonal propagation, and DNA markers are key parts of crop development. Because there are a number of coproduct, conversion, and energy product options, the genetic improvement targets vary widely. Energy targets include fermentation to ethanol, pyrolysis for production of electricity, and gasification to produce a variety of materials, fuels, and other energy products (Sheehan 2009).

Although a number of exotic species are available and many more are being tested, they pose a serious risk of spread from extensive energy plantings, which could cause broad ecosystem alterations. This risk is exacerbated by species and conventional or biotechnology-assisted genetic selection for the ability to thrive with minimal inputs and

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under highly stressful conditions (DiTomaso et al. 2007). In contrast to genetically engineered (GE) crops, the introduction of new exotic crops does not trigger automatic regulation at the federal level (DiTomaso et al. 2007). Various states may regulate exotic species as invasive or weedy, but the level of regulation is variable and far less stringent than it is for the federal regulation of GE crops.

Genetic engineering is being studied as a means to speed or supplement conventional breeding of perennial energy crops. In agriculture, GE crops are probably the most successful and rapidly adopted crop technology in history, judged by the rate and scale of their adoption. They have been grown on more than 800 million hectares in just over a decade of extensive usage (ISAAA 2007), and have brought substantial environmental and human health benefits when compared with the agricultural systems they have modified (e.g., Brookes and Barfoot 2005, Fernandez-Cornejo and Caswell 2006, Kleter et al. 2007, NRC 2010). Many of the targets for GE in biofuel crops have the potential to promote system sustainability and mitigate inherent trade-offs in food crop economics (Sexton et al. 2008), as well as increase life-cycle benefits for greenhouse gas mitigation (table 1; Sheehan 2009). Greenhouse gas mitigation can occur by modifying traits to reduce energy usage during feedstock processing, improve yields, reduce the need for tillage in crop management, reduce pest damage, and improve stress tolerances that allow crops to be grown with less water, fertilizer, or crop protection inputs per unit of product. Thus, it is reasonable to expect that the new traits provided by GE methods for perennial biofuel crops, if they can efficiently navigate the research and development pathway and obtain marketplace and regulatory approval, might have large economic and environmental benefits similar to those seen for first-generation GE crops.

However, to date, the great majority of genetic engineering has involved only a few single or stacked types of genes, two basic trait types (insect and herbicide resistance), and four species of crops (soy, maize, cotton, canola). Two GE trees have been commercialized, and two are currently undergoing regulatory review. Virus-resistant papaya is commercially grown mainly in the United States (Hawaii) and insect-resistant poplars are grown in China. Virus-resistant plums were deregulated by the US Department of Agriculture (USDA), received a positive food safety consultation from the Food and Drug Administration (FDA) in early 2009, and are still under regulatory consideration at the Environmental Protection Agency (EPA; Ralph Scorza, USDA Agriculture Research Service, personal communication, 22 February 2010). Long delays have occurred at the EPA in finalizing the deregulation of viral coat-protein events even though the agency convened a Scientific Advisory Panel (SAP) report in 2004 that focused on plant-incorporated protectants (PIPs) employing viral coat proteins (EPA 2004). The use of cold-tolerant, male-sterile *Eucalyptus* for bioenergy and pulp is currently being scaled up in precommercial field trials (APHIS 2009a); an application for full deregulation of this GE *Eucalyptus* is now in the hands of the USDA. In contrast to the majority of commercialized agricultural GE crops, there is a very wide variety of species, genes, and traits of potential value that the regulatory system may need to address (table 1; Chapotin and Wolt 2007).

Because both grass and tree crops usually have wild or feral relatives and are weakly domesticated, they can spread and persist in the environment much more readily than major GE agricultural crops such as maize, soy, and cotton in the United States (Stewart 2007). Consequently, depending upon the specific traits and the location of production, these wide pollinators may have environmental effects that are much harder to predict and manage than those of row crops. Unless researchers employ strong sterility genes or use species with histories of limited spread in a region, there is near certainty of spread beyond the farms where the GE trees or grass are first launched.

As discussed in detail below, these inherent characteristics challenge our regulatory system, which now requires detailed experimental evidence of environmental safety—under strong ecological containment—for every new gene insertion. The goal of this article is to explore the legal and

***Table 1. Genetically engineered (GE) traits under development for perennial biofuel crops.***

| Category of GE target | Traits |
|---|---|
| Modified crop physiology or product quality through modifications in the expression or DNA sequences of native genes and pathways | Form, stature<br>Growth rate, yield<br>Feedstock chemistry, structure, density<br>Abiotic stress tolerance (e.g., cold, salt, heat, nutrition)<br>Biotic stress tolerances (disease, insects)<br>Herbicide tolerance<br>Bioremediation |
| Substantially novel products or functions | Pest-resistance toxins<br>Abiotic stress-resistance proteins<br>Enzyme, material feedstock, pharmaceutical coproducts (bioreactor)<br>Herbicide resistance<br>Bioremediation |
| Biological and social facilitation | Domesticating traits of many kinds (e.g., semidwarfism, reduced response to shading, increased water or fertility requirements)<br>Male- or female-sterility-lethality systems<br>Trait expression requiring chemical trigger or postharvest treatment |

biological reasons that the US regulatory system provides such major obstacles to the use of GE as a breeding method for perennial energy crops, and then to discuss options for regulatory reform that may avoid the regulatory bottlenecks that appear inherent in the current system.

## Regulation in the United States

Unlike Europe and many other countries, the United States has not passed laws specific to GE crops and products. The United States has, however, adapted existing laws to create a complex set of rules under the 1986 Coordinated Framework (OSTP 1986), using the existing regulatory authority of three agencies: the EPA, for transgenically introduced PIPs against all kinds of plant pests; the USDA Animal and Plant Health Inspection Service (APHIS), for all crops under their authority to regulate introductions of agricultural pests and noxious weeds; and the FDA. These rules cover virtually all types of GE plant breeding, whereas comparable traits (e.g., herbicide resistance, pest tolerance) obtained through conventional breeding remain unregulated. For crops presenting more than one type of risk issue (e.g., food and environment), the agencies work together.

**The FDA.** The FDA would generally not have regulatory authority related to GE woody energy crops because these crops will not enter the food supply. However, when a transgenic energy crop also could be used for food, or when energy grasses could be fed directly to livestock, researchers and developers would be very wise to consult the FDA to determine whether the product is substantially equivalent to existing products from that crop (FDA 2001). For example, there are efforts under way to restore the American chestnut to North American forests (Merkle et al. 2007). This species could serve as an energy crop because of its very fast growth in poor soils and its calorie-rich wood. However, it also produces nuts that humans and wildlife eat. Full and timely restoration is likely to require a combination of conventional hybridization-backcross breeding and GE methods.

**The EPA.** The EPA regulates plants with genes that provide protection against any form of pest, but only if breeding employs GE methods (as this is considered most likely to lead to new types of toxicological exposure; EPA 2001a). The introduction of novel compounds, or changes to the levels of innate pest-protective compounds by way of conventional hybridization, mutagenesis, cloning, and other breeding methods, in both native and exotic species, remains unregulated. The EPA has considered, but not enacted, exemptions for genes that provide pest protection but are introduced using GE from sexually compatible species, or that result from RNA interference (RNAi; EPA 2001b), because both mechanisms are very unlikely to produce anything resembling the traditional toxins over which the EPA was originally granted regulatory authority under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). The EPA has also considered an exemption for genes that regulate growth through modification of plant physiological processes (EPA 2001b, 2001c). The EPA may assert this authority because the FIFRA gives it power to consider the ecotoxicology and human safety of growth-altering chemicals, such as hormone sprays. Although the precise contours of EPA regulation for plant-growth regulators is at present unclear, the EPA may well assert regulatory authority over any intentional GE modification of growth rate and form. In addition, the EPA may also assert regulatory authority over any other modifications that indirectly improve tolerance to any pest, such as through the expression of a new enzyme or coproduct, by classifying these enzymes or coproducts as PIPs. As the EPA has not yet asserted this expanded PIP classification, the toxicological and environmental data requirements for such classification remain undefined.

**APHIS.** Building upon existing "plant pest" authority, APHIS created a category called "regulated articles" for transgenic plants. As a result, APHIS took charge of regulating all research field trials for GE crops (APHIS 1986). The EPA has concurrent responsibility for field trials of plants classified as PIPs when they are sown on more than 10 acres, for which an experimental use permit from the EPA is required.

Under the 2000 Plant Protection Act (PPA), APHIS acquired expanded authority over "noxious weeds"; APHIS is responsible for considering any direct or indirect injury or damage to agriculture, natural resources, public health, and the broader environment. Though it remains to be established how "noxious weeds" will be interpreted in practice, APHIS has gained authority to look beyond plant pest risks and agronomic impacts to "other effects" under the PPA. The USDA is considering a number of changes in its regulations concerning transgenic plants; it published a draft environmental impact statement in 2007 (APHIS 2007a, 2007c) and draft rules for GE crops in 2008 (APHIS 2008c).

In the 2007 and 2008 GE regulatory proposals, APHIS suggested a preferred alternative to regulate all GE organisms as noxious weeds, ensuring that all GE crops would be subject to regulation. At present, APHIS has authority to regulate only those GE crops with sequences derived from plant pests, or those that are truly plant pests (e.g., a parasitic GE plant). In practice, however, all commercialized GE crops appear to have gone through the USDA for approval. Although APHIS seems unlikely to treat every GE plant as equivalent to a noxious weed, it remains unclear what a change in regulatory coverage could mean for researchers, developers, markets, and public perception.

After moderating its regulations in 1997 as a result of greater knowledge and favorable experiences with transgenic crops (APHIS 1997), APHIS has since pursued a course of greater stringency in it regulations and regulatory oversight of field trials. For example, APHIS is now proposing to end its system of 30-day notifications and require full permits for all field trials (Jones 2009). APHIS is apparently acting in response to critical reports from the National Academy of Sciences (NRC 2002), the Government Accountability Office (GAO

2008 and earlier), its own audit report (USDA 2005), field trial errors from noncompliance with permits, and pressures and complaints from nongovernmental organizations. Among the regulatory errors were a biopharm crop that comingled with harvested soybeans (Gillis 2002), a permit for large and confined field planting of herbicide-tolerant bentgrass that was found to have moved miles off site through pollen and seed dispersal (Zapiola et al. 2008), and the StarLink food recall debacle (Bucchini and Goldman 2002).

These errors also increased the regulatory oversight of perennial biofuel GE crops. APHIS reversed its earlier policy allowing notifications under strict performance standards, requiring the current higher hurdle of permits for all field trials of perennial plants (APHIS 2008a). Permitting appears to slow approval, which was particularly evident in 2008 and 2009 as the number of permit applications rose (table 2). Of special concern are the maximum issue times, which were approximately 500 days in both of those years, and included two permits for poplars issued in 2008 that required 382 and 518 days, respectively, and one in 2009 that required 478 days. In May 2010, Arborgen obtained permits to allow flowering in two sets of field trials of cold-tolerant, male-sterile *Eucalyptus* hybrids in the United States; the permit requests were submitted on 11 January 2008 and 14 January 2008 and the USDA made its decisions after 849 and 852 days, respectively (source as in table 1). Such time delays present challenges for small companies using short-term capital and a public sector that depends on grants and contracts. Worse still, we believe that the time delays for permits for many perennials are considerably underestimated compared with the averages shown in table 2; most of the species under study are trees that do not flower for several years. Where longer-term trials (through to flowering) are required, or where rapidly flowering species such as grasses are employed, permits are likely to require much more effort to process, as was observed after submission of a permit to allow flowering in poplars (APHIS 2008b). By stating that plants will be harvested before flowering, researchers ensure that permits will be processed rather quickly, as is likely to be true for the large majority of tree permits issued to date. Finally, because APHIS proposed that all perennials be put into a higher risk category (APHIS 2007a), it seems likely that all forms of perennial biofuels crops, even those with cisgenes (unmodified genes from compatible species inserted through GE methods; Schouten and Jacobsen 2008), will be required to undergo time- and resource-consuming permit applications for field trials. This would include an event-by-event regulatory review for any varieties intended for commercial use.

***Table 2. Time required by the US Department of Agriculture's Animal and Plant Health Inspection Service to issue permits for field tests of perennial plants.***

| Year issued | Number submitted[a] | Average days to issue | Longest days to issue |
|---|---|---|---|
| 1989 | 8 | 87 | 143 |
| 1990 | 9 | 52 | 187 |
| 1991 | 8 | 64 | 88 |
| 1992 | 12 | 76 | 120 |
| 1993 | 9 | 75 | 134 |
| 1994 | 11 | 58 | 104 |
| 1995 | 10 | 65 | 115 |
| 1996 | 10 | 69 | 154 |
| 1997 | 9 | 44 | 75 |
| 2000[b] | 3 | 10 | 28 |
| 2001 | 1 | 18 | 37 |
| 2002 | 1 | 57 | 57 |
| 2003 | 8 | 68 | 131 |
| 2004 | 9 | 82 | 140 |
| 2005 | 7 | 92 | 120 |
| 2006 | 6 | 63 | 92 |
| 2007 | 8 | 54 | 105 |
| 2008 | 34 | 96 | 518 |
| 2009 | 23 | 80 | 478 |

a. Data were accessed from the US Department of Agriculture Web site *(www.aphis.usda.gov/brs/status/BRS_public_data_file.xls)*. The perennial plant species in the Biotechnology Regulatory Service field test database included alfalfa, American chestnut, American elm, apple, aspen, various poplars (*Populus* species and hybrids), loblolly pine, pitch × loblolly hybrid pine, pear, sour orange, spruce, switchgrass, and walnut. Thirteen entries with a received date prior to the issued date were deleted to avoid negative values.

b. No permits for perennial plant field test permits were issued from 1998 to 1999, and thus no data were available for these two years.

*Note:* After 1997, notifications were expanded to include perennials (APHIS 2008a) for most types of field trials (1998). After 2004, APHIS began to require that all field trials of perennials obtain permits rather than notifications (APHIS 2005).

Because of the propensity for pollen, seed, or vegetative movement during research and development of GE perennial biofuels crops, there are enormous legal risks of adventitious presence from new, unapproved GE materials (Bryson et al. 2004). In the United States, two significant cases involving legal liability as a result of unapproved adventitious presence illustrate the magnitude of these risks. In the StarLink case, a variety of maize approved for feed but not for food was found in trace amounts in various foods, resulting in food recalls and related lawsuits (Uchtmann 2002). The LLRice 601 case involved transgenic rice from approved field trials that was not approved for commercial release but became comingled in trace amounts in the seed supply for commercial rice production (Vinluan 2009). Both the StarLink and the LLRice 601 cases led to the imposition of very substantial civil penalties. The LLRice case continues to result in multimillion-dollar compensatory and punitive damage awards imposed by courts as a result of lawsuits from more than 6000 plaintiffs. Thus, actual and potential legal liability for comingling must be a major factor in the decisions of researchers and companies interested in the research and development of GE biofuel crops.

### Regulatory court cases

Beginning in 2006, plaintiffs seeking to slow or limit the use of GE crops in agriculture won several federal court cases under the National Environmental Policy Act (NEPA). Courts can enjoin marketing by finding that the USDA failed to prepare an environmental impact statement (EIS) before granting approval for field trials, or before allowing the commercial release of a transgenic crop. In each instance, APHIS had prepared an environmental assessment (EA) and issued a finding of no significant impact on the environment. However, federal courts ruled that APHIS should have prepared an EIS—a much more comprehensive, detailed consideration of environmental impacts and alternative actions than an EA provides. An EIS generally requires years of study and analysis to produce a level of documentation that is sufficient to possibly withstand legal challenge.

Although NEPA is a procedural statute that does not mandate any particular substantive decision, it requires federal agencies to take a "hard look" at environmental impacts of federal regulatory decisions, such as granting field trial permits or deregulating transgenic crops (Bryson 2008). The NEPA cases have raised two significant legal issues: (1) For transgenic crops, does an EA satisfy the hard look, or must the agency always prepare an EIS? (2) What must the agencies account for when writing an EIS? Should they consider direct and indirect environmental impacts and "interrelated" economic impacts such as possible effects on international trade, marketing, and farm economics (e.g., effects on farm sizes and farming styles)? Would this consideration include consumer preferences like the ethical views of a minority of highly concerned consumers? The ruling in the case of herbicide-tolerant alfalfa, which was first authorized and then withdrawn by court action while an EIS was prepared, suggests that such social considerations now have legal precedence (Peck 2008).

When a transgenic energy crop comes before a federal agency, either for a field trial permit or deregulation, the agencies must be very cautious when deciding whether to prepare an EA or an EIS. If they choose an EIS, they must carefully analyze what environmental, economic, social, and consumer issues to consider before making a regulatory decision. Should agencies look at both the effect of the new trait and its specific phenotypic effects on the environment and also all the environmental and economic issues associated with growing the crop? For example, in the case of cold-tolerant eucalyptus (APHIS 2009a), highly complex, scale-dependent, and potentially unpredictable effects on biological diversity, invasiveness, hydrology, and fire ecology must be considered that do not apply to a cold-tolerant, conventionally bred species. Because of the complexity and scale dependence of the environmental questions, it is virtually impossible to answer them adequately without large-scale commercial plantings and associated monitoring and "adaptive management" (cf. Auer 2008, Firbank et al. 2005), nor is it possible to fully understand the life-cycle environmental benefits of species as perennial energy crops (Sheehan 2009). The USDA proposed an option for provisional deregulation that would allow such scale-appropriate research (i.e., where final approval is subject to further research and monitoring) in its programmatic draft environmental impact analysis (APHIS 2007a), but it was subsequently dropped. In addition to the formidable containment hurdles to research and development that we further discuss below, these legal issues about the meaning and scope of NEPA are likely to be litigated for years to come, creating uncertainty, insecurity, and cost disincentives for researchers and developers of transgenic energy crops.

### Consequences of regulations for field research and containment technology

The regulations in place, forthcoming, and those that have been imposed by legal actions result in the presumption that all forms of GE trees and grasses are "plant pests" or "noxious weeds" until extensive experimentation and associated documentation "prove" otherwise. This means that strict confinement of propagules from GE grasses or trees will be required during all stages of research and development until the GE plant is fully deregulated. Because all GE products must enter the normal crop breeding stream at some point to ensure the GE traits are useful under agronomic conditions and do not impose adverse effects on other traits, is strict confinement indeed compatible with real-world breeding and environmental assessment of biofuels crops?

For most of this discussion, we assume that the GE crops involved will be able to establish themselves in the environment and cross with wild or feral relatives, although special cases may occur where high levels of containment are biologically provided as a result of the biology of the species in a new environment, hybrid or triploid infertility (e.g., some *Miscanthus* and *Eucalyptus* genotypes), or the use of genetic containment technology (e.g., transgenic male sterility, which has been demonstrated to be highly effective in *Pinus* and *Eucalyptus*; Maud Hinchee, Arborgen, personal communication, 25 May 2010). If reliable and efficient technologies for vegetatively propagated biofuel crops are developed, as we expect is possible given the many options available (Brunner et al. 2007), they might solve most of the problems from dispersal of these kinds of GE biofuel crops, as well as greatly reduce the threats of invasiveness from new exotic species. Numerous researchers have pointed out the ecological value of containment technologies for these purposes (e.g., Ewel et al. 1999, Snow et al. 2004, Chapotin and Wolt 2007, DiTomaso et al. 2007, Auer 2008).

However, most of the currently available systems, conventional and transgenic, are unlikely to be perfect when considered over long time frames and large spatial scales, or at least their success has not yet been proven one way or the other. A great deal of further development and field verification of containment technology is needed to understand these systems' efficacy to a legal standard. Therefore, even where such technology is extremely efficient, and provides a large reduction in risk over currently planted exotic forms, such "sterile" varieties may still raise the same issues for regulatory bodies and courts as we explore below for fully fertile crops. A recent survey of forest scientists about how regulations affect the development of transgenic forest biotechnology in the United States identified the development of "application-oriented research in…containment options and efficiency" as the number-one research priority (Strauss et al. 2009a). However, the development and field verification of containment technology performance is itself made extremely difficult by today's process-based regulations, which include a ban on field trials with GURTs (genetic use restriction technologies) that has been recommended by parties to the Cartagena Protocol on Biosafety (box 1; Strauss et al. 2009b).

### Field testing in plant breeding

It is widely accepted that all forms of plant improvement, both conventional and biotechnological, require extensive field evaluation to determine performance and impacts under realistic conditions (table 3; review in Strauss et al. 2009b). The physiology of plants in laboratories and greenhouses is distinctly different from that under field conditions, which are more stressful, biotically complex, and highly diverse in time and space. Thus, establishing whether a new biotech trait is useful, and what levels and forms of a new trait are useful, requires extensive field experimentation.

Evaluations of a crop with a new GE trait would normally proceed thorough four general stages: (1) Lab and greenhouse studies are conducted to observe, under controlled conditions, the existence of a desirable trait imparted by a gene in a model species and a model crop variety. (2) Limited field trials occur in one or a few model varieties and environments to see whether the trait persists in the field to a useful degree, or has adverse consequences for other traits. Most genes that pass stage 1 fail at this second stage. (3) Researchers then test several different forms of the gene that might have different promoters to vary expression pattern and level, including a

**Box 1. Unintended effects of process-based regulations in the United States: The birth and death of an ecological containment research program in poplar trees.**

The establishment of progeny from genetically engineered (GE) trees in the environment and gene flow from GE trees to wild and feral relatives have long been an ecological and regulatory concern (James et al. 1998). Long-standing efforts have attempted to introduce sterility genes to reduce risks from dispersal of genes in the environment, which builds upon the considerable progress in the basic understanding of the genes that control flowering (Brunner et al. 2007). Although there are numerous promising gene and promoter options derived from results from model organisms such as *Arabidopsis* and short-term evaluations in the greenhouse, so far there have been very few studies of field performance of containment genes in any crop species (Auer 2008). Field studies are essential to determine the degree of sterility and stability in the diversity of environments under which the crops will be grown. For trees, this would generally require growth over a rotation (or at least through several flowering seasons) in a number of environments. The risks resulting from escape of incomplete sterility genes from research sites are extremely low because of their small number compared with normal fertile trees usually grown in the area (i.e., genetic swamping from natural sources), and because these traits act to reduce fitness and spread by limiting their own replication. However, because all products of the GE method are considered to be potential plant pests—even genes encoding fitness-reducing traits, which for hybrid poplar would appear to reduce the ecological risk of currently used exotics and interspecific hybrids—trees must be confined during all stages of research and development prior to deregulation by the US Department of Agriculture Animal and Plant Health Inspection Service. As a consequence, such flowering transgenic trees are excluded from field trials where they can establish or mate with wild relatives, excluding them from being grown in the most ecologically relevant study sites. Even in the case where the genotype used cannot mate with nearby trees or spread from seed (see the figure; APHIS 2008c), strict containment and removal are required. The costs of growing, monitoring, and removing trees, and complying with federal regulations over the time span of a flowering modification experiment (approximately 10 years), have led to dissolution of this type of field research program (cf. APHIS 2008c).

*View of a clone bank of genetically engineered (GE) poplars with approximately 1000 transgenic insertion events composed of a wide variety of containment genes. The trees are ready for field evaluation through to flowering. Although the poplar genotypes used do not spread or mate with wild relatives in the region (APHIS 2008b), current regulations require monitoring and complete removal of trees from the environment after the trial solely because the GE process is presumed to be a risk or harm. As a consequence of the regulatory restrictions, protracted legal risks over the many years required to study flowering, and associated costs of compliance, these varieties—produced with considerable industry and government agency investments over many years—have not been planted so as to allow observation of their flowering within the United States.*

*Table 3. Steps for commercializing transgenes for alfalfa (McCaslin 2002), but showing the estimated time for its application in switchgrass. Some work can be done concurrently, but other issues, such as regulatory delays due to political controversies or lawsuits, may require considerably more time than estimated.*

| Step | Description | Estimated time (years) |
|---|---|---|
| Vector construction | Selection of the appropriate promoter, transit peptide, leader sequence, terminator, and so on. Intellectual property licenses for future commercialization obtained, which can require protracted negotiation. | 0.5 to 2.0 |
| Transformation | Transformation of elite genotypes using *Agrobacterium* vectors or particle bombardment to achieve a high frequency of simple, single-copy insertions to expedite breeding and regulatory approval. | 0.5 to 2.0 |
| Confirmation and characterization | PCR (polymerase chain reaction)–based tests, sexual stability of the transgene, inheritance and Southern blot analysis. | 1.0 |
| Proof of concept | A multistage process that usually begins with an analysis of the initial transformant ($T_0$) plants in the greenhouse or growth chamber, followed by multiple location field trials to confirm the desired phenotype; conducted under regulated permits by the US Department of Agriculture (USDA) and APHIS, its Animal and Plant Health Inspection Service. | 2.0 to 4.0 |
| Event selection | Evaluation of many events for the desired transgenic phenotype, substantial equivalence estimates for agronomic and forage quality traits, and "clean" molecular inserts. Only a small fraction of the $T_0$ plants will advance using these criteria. One or more "commercial events" will need to be identified and submitted for regulatory approval. | 2.0 |
| Trait integration and sorting | Backcrossing the "commercial event(s)" of the transgenic trait into elite commercial lines for key commercial target markets (under regulation). | 2.0 to 4.0 |
| Product development | An extension of the trait integration program that includes extensive field evaluation of transgenic populations under regulatory permits, selection of parent clones, and the agronomic evaluation of transgenic experimental varieties while maintaining strict segregation from varieties that are not genetically engineered. | 2.0 to 5.0 |
| Regulatory approval | Before US commercial release, all transgenic events require approval by the USDA to confirm agronomic safety and, if a plant-incorporated protectant, by the Environmental Protection Agency to confirm environmental safety. If the plant product is or may be a food or feed product, developers consult with the Food and Drug Administration to confirm food and feed safety. Researchers must produce molecular characterization of the transgenic insert and the flanking genomic DNA; ecological evaluation of the transgenic trait on nontarget populations (i.e., wild relatives or feral plants), and data that support the substantial equivalence of the transgenic plant compared with nontransgenic plants for key traits. | 4.0 |
| Commercial release | After regulatory approval, commercial seed of transgenic varieties can be marketed. | 1.0 |
| **Total time for the United States** | | **15.0 to 27.0** |
| Trade authorizations | Regulatory approval may also need to be sought in other countries to comply with the Cartagena Protocol on Biosafety and diverse national regulations, which often require repetition or expansion of US-based studies already performed. | 2.0 to 5.0 |
| **Total time international** | | **17.0 to 33.0** |

large number of different insertion events to identify those with favorable expression patterns. This stage also normally includes an initial analysis of agronomic properties, albeit in a limited sample of commercial varieties and environments. (4) The gene is moved into many different commercial genotypes and is tested in a wide variety of environments for the new trait and agronomic properties. These tests are essentially normal breeding trials aside from the required regulatory approvals, monitoring, use of buffer zones, and other steps required to assure segregation from actual commercial varieties and products. As evidenced by the many cases of adventitious presence of unapproved GE varieties that have entered the food supply at a low level, this is perhaps the most risky step in crop development when using transgenes.

The number of gentoypes that must be tracked and segregated is large at all development stages. Stages 2 and 3 will often involve about five transgenes, 20 insertions, and 10 replicates of that insertion over five environments and two genetic backgrounds (approximately 10,000 experimental units), whereas stage 4 is likely to involve at least two transgenes and five events each, tested in 10 or more genetic backgrounds over 10 or more environments (approximately 1000 experimental units), but with much larger, nearly commercial-scale plantings of each. There are usually hundreds to thousands of other genotypes simultaneously under evaluation at the same locations for general plant breeding goals that must be kept free from any possible comingling. Although the details will vary widely among crop types, for highly diversified crops such as wheat the above scenario substantially understates the numbers and logistical difficulties (James Peterson, Oregon State University, personal communication, 22 February 2010). Thus, the tracking of all of the inserts, and accounting for the containment of each, presents a huge logistical problem for breeders, even in the absence of flowering.

### Gene flow into the environment during field studies

Gene flow through pollen and seed production, and, for some crops, vegetative movement by natural causes and farm equipment, presents an even bigger problem. Although the economic product of biofuel crop trees and grasses is vegetative matter, not seeds, reproduction may occur during trials. Dispersal curves are often leptokurtic, meaning that although a large and often dominant proportion of propagules disperses close to the source, there is a very long tail that can extend very far, often associated with rare events such as storms that move propagules long distances (Nathan 2006). The likelihood of a small amount of long-distance movement of pollen (e.g., tens to thousands of meters) by wind and some animal pollinators is therefore very high (e.g., for trees see Slavov et al. 2004). Seeds, when small or moderately sized, can also move long distances under the common windy and stormy conditions in most areas proposed for biofuel crops. Dispersal of fruits, such as by birds or associated with movements of mammals, can also be extensive.

Effective confinement of propagules therefore generally means the complete prevention of flowering, through GURTs or manual bagging over all flowers on every experimental plant. Manual bagging is extremely difficult and costly for large-scale plant breeding of any crop, and may be too risky given the legal consequences of comingling discussed above, especially for public-sector breeders or small companies (Vinluan 2009). (The LLRice 601 case discussed above, in which costly civil liability was imposed on Bayer CropSciences and researchers at Lousiana State University as a result of authorized field trials that led to comingling of research genes with the commercial seed supply, is likely to severely constrain or eliminate the many cooperative breeding programs between biotechnology companies and research universities.) Because of the large size of most trees, it is virtually impossible to remove or bag all flowers on large trees such as poplars once they are beyond the small-scale field trial stage and have been moved into larger-scale field evaluation and variety development (stages 3 and 4 above). Despite this challenge, biofuel trees can present some substantial advantages over grasses in that they normally do not flower for several years, and might be used in coppice-style (cycles of stem harvest followed by resprouting from roots), short-rotation biofuels crop systems with a complete absence of flowering (e.g., harvest every one to three years). However, for coproduct (wood and energy) systems, or in cases where trees might flower precociously due to unusual environmental conditions, serious legal implications might repel potential breeders or companies from attempting even a coppice operation.

Were efforts not required to completely prevent gene dispersal, it would be quite feasible to establish isolation distances to keep dispersal at very low levels. For example, data from three experiments in southern Oklahoma (Wang et al. 2004) demonstrated that the maximum effective travel distance of transgenic tall fescue (*Festuca arundinacea* Schreb.) grass pollen was 150 meters (m), indicating that the isolation distance of 300 m required by the USDA is enough to prevent the vast majority of transgene flow to neighboring plants in small-scale field trials. This research also demonstrated that growing transgenic plants in the downwind direction will not affect upwind conventional breeding activities, if done at sufficient isolation distances. However, if a legal assurance of zero gene flow were required, these distances could be impracticable for research and commercial-scale field trials. In general, if the goal is for transgene frequency level near the source to be approximately 0.1% to 5.0% (the exact level depending on the scale of release, the familiarity of the gene, and benefit-risk considerations), a very wide variety of strategies could be used to reliably and practically manage gene flow.

## Environmental studies and containment

The same problems of scale and containment occur with respect to environmental studies, but they are generally more problematic. Here the goal is to mimic, as much as possible, both agronomic and wild conditions and their substantial variances so the consequences of a new transgene for plant fitness, invasiveness, population increase, and nontarget effects can be meaningfully assessed when compared under agronomic practices and for wild and feral plant communities. It is critical to include carefully chosen controls, such as a wide range of nontransgenic genotypes, to obtain socially as well as ecologically useful results about the new risks and benefits of the transgenes (cf. IFB 2007, NRC 2008). Ideally, this work should be done during variety development, so that the most beneficial and least maladapted or harmful transgenes and events are ultimately chosen for commercialization. For poplar and many other pioneer species that require very specialized ecological conditions to regenerate at all, mimicking natural conditions while avoiding complete experimental failure is a major challenge (box 2; e.g., DiFazio et al. 2004).

In simple cases, such as those in which the transgene has a very discrete and largely genotype-independent effect (e.g., herbicide resistance), it may be possible to conduct limited field studies and reasonably model the ecological effects of broader use. However, for complex ecological phenomena such as plant fitness, models are generally considered unreliable, and often dangerously misleading, unless validated by extensive field studies. For second-generation transgenes that have more complex effects on plant traits (e.g., modified salt and drought tolerance, modified lignocellulosic chemistry, and modified nutrition and growth rate), the ecophysiological effects on plant physiology, nontarget organisms, and plant fitness will be extremely hard to discern without extensive field studies conducted across many environments and over many years. How these can be carried out prior to full deregulation in sufficient detail to comply with a likely NEPA legal challenge, and at sufficient rigor to withstand scientific scrutiny (cf. Auer 2008, Firbank et al. 2005), appears to be an insurmountable hurdle.

Given the high costs and special legal conditions required for such work, a major public-private effort is needed. Researchers presented the rationale for such an approach,

**Box 2. Switchgrass breeding with a genetically engineered trait is intractable under current regulations.**

Switchgrass (*Panicum virgatum* L.) is a perennial, warm-season prairie grass native to most of North America. It is currently used for hay, pasture, and conservation purposes. It has also been identified by the US Department of Energy (DOE) as an herbaceous, dedicated bioenergy crop as a result of its ability for high yields, environmental enhancement characteristics, and growth on low-input, marginal cropland (McLaughlin and Kszos 2005). Improving the bioenergy feedstock value of switchgrass through molecular breeding is relatively new (Bouton 2007, 2009). The main traits slated for improvement include biomass yield, seedling establishment, abiotic and biotic stress tolerance, and feedstock quality (i.e., higher digestibility and lower lignin; Bouton 2007, 2008).

The application of genomic and transgenic molecular tools to supplement and enhance traditional plant breeding models is under way in switchgrass. Effective tissue culture regeneration methods are available, and transformation can be successfully achieved using both microprojectile bombardment and *Agrobacterium* protocols. The application of transgenic technologies usually affects the normal breeding model at three central phases: (1) development of unique parental plants, (2) selection and breeding, and (3) testing. Commercial deployment of transgenes has not been accomplished in switchgrass, but the Roundup Ready® transgene has been commercially deployed in alfalfa, another perennial herbaceous forage crop, and the steps for this crop's development are directly applicable (table 3; McCaslin 2002). Since the commercially ready Roundup Ready® event was identified, 10 years have been spent in the regulatory process; it has been six years since the petitioning of the Animal and Plant Health Inspection Service for deregulation (Sharie Fitzpatrick, Forage Genetics International, personal communication, 16 December 2009). Therefore, the regulatory time period projected for switchgrass in table 3 seems logical (assuming no requirement for Food and Drug Administration approval as an animal feed). As a consequence of the regulatory outlook, The Noble Foundation, a nonprofit, agricultural research organization, currently is unwilling to invest the resources or gain the independent expertise to navigate the regulatory process. While the foundation has, and may continue, to participate in aspects of transgenic research (e.g., basic studies and limited field evaluations), it will be in collaboration with entities willing to share cost or lead the regulatory effort. The high cost of transgene deregulation, along with the time and resources required with little certainty of actually achieving deregulation, have modified the organization's strategic goals to focus mainly on developing genomic tools to assist its conventional breeding efforts (Steve P. Rhines, Vice President, General Counsel and Director of Public Affairs, The Samuel Roberts Noble Foundation, personal communication, 27 May 2010).

in one case called GEONs (genetic earth observatory networks—loosely and somewhat humorously modeled after the National Science Foundation's National Earth Observatory Network), at a National Research Council (NRC) workshop on GE plants (NRC 2008) and at an Institute of Forest Biotechnology (IFB) workshop on ecological effects of GE trees (IFB 2007). GEON requires the establishment of a network of sites at which a variety of genetically modified tree species, containing a variety of genes and traits, are studied for their broad ecological effects over many years. However, neither the NRC nor the IFB could define a path forward that was practical, affordable, ecologically relevant, of regulatory value, or able to comply with current zero-tolerance regulations for gene flow while still achieving its scientific objectives.

## Toward regulatory reform

The fundamental contradiction embedded in our regulatory system is that although leading scientific and environmental organizations support a "product not process" and "case by case" view of GE crops (reviewed by Strauss et al. 2009b), USDA and EPA regulations use the process of GE as the trigger for extensive study and documentation to establish that there will be no "unreasonable effects" before any scale of uncontained environmental release—even for research—is allowed. Although this policy may sound precautionary and prudent, as discussed above it has a crippling effect on biofuel crop development using GE methods. This approach essentially removes GE as a breeding tool from the very crops that need it most given their difficulties in conventional breeding. It also removes it from the roster of biofuel crop types and traits that many governments wish to emphasize most because of their anticipated environmental and economic advantages.

There are several biological rationales for process-oriented regulatory policy, including the sentiment that the environmental effects of genes should be studied before their release and use. This rationale also emphasizes that genes, which can move widely and reproduce themselves without further human agency, particularly in weakly domesticated species like perennial biofuel crops, are presumed to be high risk solely because of their ability to spread and method of genetic modification. Additionally, the harms from release of genes are often analogized with those from invasive exotic species, largely ignoring the economic and environmental benefits provided by such species and the low frequency at which exotic species become significant problems (cf. Brown and Sax 2007, Sagoff 2007, Gozlan and Newton 2009, Sheehan 2009). This line of thinking also equates a species with one or a few transgenes to an exotic, invasive species, even though a miniscule portion of the genome is novel in comparison with most of the widely publicized, ecologically novel invaders. Finally, the rationale often assumes only negative consequences from the presence of a transgene that might improve fitness and thus increase in frequency in the wild (e.g., Chapman and Burke 2006), and ignores potential benefits that such transgenes might also bring, such as increased resistance to disease and greater forest tree diversity. To date, exotic plant species have had strong and predominantly positive effects on biological diversity. Very few extinctions have been observed, even on islands (Brown and Sax 2007, Sax and Gaines 2008). Thus, a policy that avoids all releases of transgenes during research because it considers them analogous to harmful invasive species and harmful gene flow is unwarranted, and imposes a requirement from which conventional breeding is exempt even when it poses identical risks and benefits (e.g., herbicide- and pest-resistance genes), and even where exotic germplasm is employed.

We strongly believe that carefully designed environmental evaluations of new plant varieties, however they are produced, are essential if crop breeding is to help rather than retard the development of a vigorous biofuels industry that delivers bona fide environmental benefits. A strong industry will contribute positively to greenhouse gas mitigation and other environmental and economic goals. However, the current legal and regulatory situation places severe constraints on both the ability to develop GE crops at all, and then on the performance of adequate environmental studies to inform regulatory and other social decisions about their use. We believe that there is a smarter way that better balances the desire for caution with the pressing need for superior crop varieties and that results from the use of all crop-improvement tools. We propose the following actions:

**1. Focus regulatory requirements on defined risks.** We agree with recent arguments that the regulatory system needs to move away from its current trend toward unbounded and vague environmental inquiries, and instead specify focused and reasonable risk hypotheses for regulatory science to address during the problem-formulation stage of risk assessment (Johnson et al. 2007, Raybould 2007). A recent example of continuing unbounded regulatory efforts can be seen in the EPA proposal brought before a SAP in 2009 for data requirements where there is gene flow from PIPs to wild relatives (EPA 2009). The proposal, supported by the SAP in the final meeting minutes despite much testimony to the contrary, calls for broad investigations into gene flow and its effects for PIPs where there is any gene flow to wild relatives. There was no call for substantive bounding of required studies based on the type of gene and its source or novelty, the possible ecological and environmental benefits of gene flow for helping species to cope with serious climate and biotic stresses, or of the great opportunity costs imposed by the mandatory data requirements for socially valued projects that are difficult and require long time periods (e.g., restoration projects such as genetic engineering of pest-resistant trees). Asking for broad scientific studies without clear, focused, and near-term testable hypotheses in an area of high controversy rarely resolves or advances debate, but instead provides fodder for further ideological combat (Sarewitz 2004). Risk hypotheses should be directly relevant to substantive novel risks that are specifically linked to newly added genes when considered in relevant farming and affected natural systems. Improbable risk hypotheses and calls for broad efforts that feign the ability to confidently predict ecosystem evolution after a specific genetic perturbation should be eliminated or greatly reduced in scope of required analysis at the problem-formulation stage. Likewise, risk assessments that assume that current ecological communities are optimal, and that it is feasible to conserve them long into the future, could also be disregarded as untenable in the modern world.

**2. Use scientific criteria for design of categories for a low-level presence (LLP) system.** The legal risks and costs of field testing could be greatly reduced if LLP levels could be categorically set by regulatory agencies using the criteria of risk, benefit, and familiarity. Field tests that might qualify for expedited treatment, including exemptions, are the low-risk tiers that have been identified in a number of reports, including those by the USDA in its EIS draft (Barton et al. 1997, Hancock 2003, Strauss 2003, Bradford et al. 2005, APHIS 2007a). Cisgenic and intragenic varieties (Rommens et al. 2007, Schouten and Jacobsen 2008) are obvious candidates for complete exemption or notification. For such modifications, the publication of simple best management practices (BMPs) that allow levels of LLP congruent with current plant breeding practices would be appropriate. Similar provisions could greatly promote the use of "genomics-guided transgenes" (Strauss 2003), and thus promote the use of native or homologous genetic information, such as for improved processing capacity of feedstocks for biofuels through lignin modification (Boerjan 2005). As discussed in detail by Bradford and colleagues (2005), many familiar GE tools (e.g., promoters, selectable markers, reporter genes, *Agrobacterium* borders, and other sequences), as well as the mutagenesis process from transformation itself, should also be exempted because of the sufficient experience with them during conventional and transgenic breeding, as well as prior regulatory decisions. More complex traits, such as those very likely to substantially promote fitness in wild or feral environments and where it is clear that such effects would be predominantly harmful rather than beneficial, could be also be managed under management practices that allow workable levels of LLP once sufficient familiarity or experimental data are provided through a petition process—one that might be similar to the current APHIS permitting process. Bioindustrial products could also be exempted or considered for high LLP if their novelty were low, if their expected effect on fitness were small or negative, or if they were not highly toxic to nontarget organisms (e.g., familiar enzymes and nontoxic and biodegradable biopolymers). With a rational LLP policy, the current situation—where applicants are asked for extensive environmental data under strong confinement for all GE products because of their method of creation—could be fundamentally changed.

**3. Create an early stage LLP management system.** To legally identify which genes in which crops will and will not be permissible for noncontained field research under a revised, scientifically designed LLP policy, we need a system—perhaps analogous to the notification system now in place—that provides for expedited approvals and some kind of general standards of conduct for allowable research (e.g., maximum test sizes and numbers for various species and regions; BMPs for different species to reduce but not eliminate all gene dispersal; and categories of allowable genes based on risk, benefit, homology, and familiarity). The regulatory regime could adopt various approaches to stewardship and BMPs as a condition for allowance of LLP (e.g., APHIS 2007b). As long as the BMPs were followed, there would be no requirement for tracking gene dispersal nor legal liability for gene movement, similar to the case for conventional breeding. Indeed, such BMPs can be helpful to farmers, neighbors, and the public without being commercially impracticable. APHIS has just proposed a pilot project in quality management with this goal in mind (APHIS 2009b). Voluntary stewardship to reduce undesired economic impacts has worked well in the US soybean sector. Agronomic standards, such as refugia implemented through contractual arrangements between seed developers and farmers, have proven effective at impeding the evolution of resistant insects. Farmer cooperation through coexistence plans and grower districts (such as exist in the northwestern states for canola and industrial rapeseed) are widely acknowledged as feasible and effective (e.g., Redick 2004, Kershen and McHughen 2005).

**4. Clarify the role of NEPA and the Convention on Biological Diversity (CBD).** We need clarity about where NEPA falls with respect to GE in research and development, and which social and environmental criteria are relevant for consideration and which are not. Ultimately, given the many trade and gene-flow issues surrounding perennial biofuel crops, a similar level of clarity is also required by the CBD and other international agreements. Without such clarity, even with a biologically rational system such as we have proposed above, few companies will see fit to take the risks of navigating a costly, slow, and uncertain legal system.

## A leadership challenge

Unfortunately, because of the many layers of legal restrictions—from those involving international trade to national, state, and local ordinances—the regulatory thicket is deep and thorny. Ameliorating this problem may well require new laws in the United States and overseas, or a fundamental court precedent that stops the penalization of the GE process, thus finally enshrining into law the "product not process" principle—one scientific reviews have continually supported (e.g., NRC 2002, Snow et al. 2004). Such a change would require regulations and legal challenges to be on the basis of physical rather than perceptual or economic harm from the simple presence of GE in food or organisms in the environment. This change will be especially difficult to enact in the area of international trade, given the hesitancy of many European Union countries to accept any GE products in domestic agriculture and food. It will also be very difficult given the special treatment of GE in the CBD, and its many costly, ambiguous, and poorly founded biological provisions (Strauss et al. 2009b), most notably for liability and redress. In short, solving these problems will require new ways of thinking and strong scientific and political leadership to move us toward a regulatory system that enables, rather than arbitrarily blocks, the use of GE as a tool to accelerate and diversify the breeding of perennial biofuel crops.

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Thomas P. Redick has no financial interest, through investment or professional representations (e.g., through clients such as the United Soybean Board, a grower organization), in companies developing genetically modified plants.

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