

Regulating Biotechnology as though Gene Function Mattered

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Although nearly every aspect of agriculture with genetically engineered crops seems to generate some kind of controversy, scientists agree on one score: The diversity of genes, the phenotypes they give rise to, and the biology of crops make generic statements of risk or benefit—even generic approaches to risk assessment—useless. It all depends. This complexity has prompted most regulatory schemes to consider genetically engineered crops case by case.

But this practice—evaluation on a crop-by-crop, trait-by-trait basis—imposes serious costs on society. It lends credibility to the idea that all genetically engineered products are more dangerous than conventionally bred crops. (If they are not more dangerous, many people reason, why would governments choose to intensively regulate *all* of them?) Moreover, the requirements for data on safety are much the same for familiar types of genes as for those transgenes that are truly novel. The consequent high costs may effectively preclude the development of many small-market, genetically engineered crops that could, cumulatively, have enormous social benefit.

In this issue of *BioScience*, Jim Hancock suggests a sensible way to improve the process of assigning risk, and thus implicitly to improve regulatory schemes—namely, place the emphasis on the transgenic trait, the crop host, and the presence of wild relatives (Hancock 2003). He also proposes that large classes of transgenic crops, depending on their gene and crop biology, be exempted from requirements for most kinds of environmental studies. Although no categorical system will be

perfect in the face of the extraordinary variation inherent to genetics and agriculture, Hancock makes some important recommendations for ways to move forward. Several of his conclusions are worthy of repetition as well as scrutiny.

New compartments are needed

There is no such thing as sustainability, at least in the sense of stability, when it comes to breeding. The world keeps changing, society's food and fiber needs keep changing, pests and climates keep changing, and thus breeders keep their jobs. If the kinds of costly requirements that are in place for genetically engineered crops were to be imposed on the inherently incremental process of breeding—if each field experiment were tightly regulated and each new variety required years of testing and government approval—there would be no breeding. Most scientists would agree that such regulations would not serve society's needs well at all. But genetic engineering, by making it possible to transfer genes across vast taxonomic boundaries, enables the production of new products and thus new risks. The question facing society is what kinds of new compartments can be constructed to allow the breeding process to accelerate in the light of genomics knowledge and genetic engineering, while avoiding or restricting those applications with high risks because of their ecological or toxicological novelty. Hancock in effect proposes subcompartments of genetically engineered crops to facilitate regulatory consideration. His proposal follows the “product not process” paradigm that the ecological and genetic science communities have long

insisted on (NRC 2002), but rather than considering every new transgene–crop combination independently, Hancock sorts them into biologically rational groups.

Let “domestication genomics” go forth

Hancock suggests that some kinds of genes in some kinds of crops need to be highly restricted or even forbidden. But he also recognizes that large classes of genes have a high level of environmental safety. He states that “genes with detrimental effects will be selected against in the natural environment and will not spread. Many of the traits associated with crop domestication fall into this category.... Examples of transgenes that fit into the detrimental category are male sterility, altered fiber quality, changes in lignin biosynthesis, and altered fruit ripening and storage characteristics.” He argues that such traits will not spread significantly because of their deleterious effects, and thus will have little environmental impact on wild plant populations. He also points out that there are some cases where wild populations of native plants are very small and thus could be subject to swamping, and that these might require special protections. However, in most cases domestication traits present a large frontier that genomics-empowered genetic engineering (Strauss 2003) could move along with little or no regulatory oversight. These traits have also been the subject of modification by breeding in many crops and so are familiar in their phenotypic effects.

Breeders deserve respect

Breeders continuously induce the expression of rare mutations through inbreeding. They also reassort genes and chromosomes brought together by hybridizations among diverse, and ecologically and toxicologically distinct, populations and species. Yet breeding's record is one of socially acceptable levels of environmental and food safety. Hancock states that "in spite of many substantial advances in breeding for resistance to pests, drought, cold, and salinity, studies have not yet shown that the native fitness of the wild species was noticeably changed through hybridization with the crop progenitor." This is probably why there have been no calls to impose significant regulations on plant breeding.

By selecting integrated phenotypes and drawing on alleles from hundreds of populations and often from many species, breeders are tapping into variation in untold numbers of metabolic and developmental pathways. In contrast, genetic engineers often try to modify one or a few genes toward some laboratory version of a sought-after trait such as drought resistance. And because the regulatory genes that tend to be of most interest to genetic engineers for modifying physiology are deleterious unless regulated precisely, the record to date is largely one of impaired, rather than improved, plant performance (e.g., Chen and Murata 2002). This suggests that genetic engineers will have to work extremely hard if they are to move agronomic traits further than breeders, now empowered by candidate gene and marker-aided selection, are able to do. This should both humble genetic engineers and inspire a relaxation of government regulations when genetic engineering methods are used to modify native or homologous genes and pathways.

Natural selection also deserves respect

Hancock states that "transgenes that change the environmental tolerance of a species or alter its patterns of growth and development could result in dramatic adaptive shifts and have a major

impact on fitness. For example, juvenility in trees might be reduced by overexpression of a regulatory gene such as *LEAFY*,...allowing for earlier reproduction and possibly greater overall reproductive success because of more frequent flowering." Sounds scary, but this kind of thinking assumes there is some dearth of diversity for these traits in the wild. In fact, virtually all wild species house large amounts of genetic diversity in stress tolerance and developmental traits. With respect to flowering, there are few aspects of development more important to the fitness of a plant than the decision to reproduce. This decision is therefore subject to an extraordinarily complex web of internal and environmental regulatory networks (Levy and Dean 1998). As tree breeders know, there is plenty of genetic diversity in time to flowering, should natural selection see fit to change it. However, they also know that dramatic changes in time of flowering, such as those that *LEAFY* might impose, would create a tree unable to grow rapidly and thus unable to compete successfully for light, which means it would die after a short time. It is hard to beat natural selection unless you have a real functional novelty to offer. And even then, to have a large impact on a species and its associated organisms, the novelty must spread widely—which means that it must continue providing a selective advantage when it becomes common (i.e., it is not likely to be rendered useless by evolutionary, behavioral, or climatic changes). This is unlikely to be the case with any of the engineered pest resistance genes in commercial use today.

Scale matters

Hancock argues that the details of gene flow are largely irrelevant to risk considerations, because genes will eventually get out. He states that "the factors limiting gene flow between compatible relatives can be largely ignored, as transgenes will eventually escape into the natural environment if there is a compatible relative near the transgenic crop,...unless the transgenic crop produces no viable gametes or has a system

incorporated that prevents embryo viability." However, it is logical to expect that the scale of introduction is an important determinant of the probability of spread, and this seems to be the case for invasive exotic species. Species inserted into novel environments multiple times appear to have a higher chance of successful establishment (Sakai et al. 2001). We can also predict with high confidence that the genetic confinement systems Hancock refers to will not provide absolute containment. Are systems that provide 95 percent confinement adequate? What about 99.999 percent? Most scientists would agree that systems that highly restrict gene flow would make the risks of most transgenic crops far more biologically acceptable; however, how much gene flow is tolerable will depend on the function of the dispersed genes, the characteristics of the recipient environments, and the time span under consideration. Very modest amounts of gene flow restriction might be adequate for modifications to native or closely homologous genes, or where domestication traits are produced. The rate of gene flow *does* matter, but the difficulty is in deciding how little is little enough. Unfortunately, for some novel genes, estimating "negligibility" is anything but a little task.

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