The Nature of Change: Towards Sensible Regulation of Transgenic Crops Based on Lessons from Plant Breeding, Biotechnology and Genomics

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> *...in a vast number of cases, we cannot recognize...the wild parent-stocks of the plants which have been longest cultivated in our flower and kitchen-gardens.... breeders could never have expected or even have wished to have produced the result which ensued.* —Charles Darwin (1859)

With these words in his *Origin of Species*, Darwin made clear the power of selection and plant breeding to alter the appearance and usefulness of crop plants. The selection of plants with improved agronomic traits, along with improved agricultural technology, have been key factors in maintaining agricultural productivity during exponential growth of the global population over the past two centuries (Evans, 1998).

With the advent of genetic engineering, transfer of DNA between species became possible, thus vastly increasing the power of genetic modification. At the same time, genetic engineering captured the public's attention in a way that more conventional plant breeding techniques never did. Genetic modification has come to be feared in its own right, particularly in Europe and in several developing countries. The result is an onerous patchwork of regulatory systems around the world. The regulatory requirements all too often mirror concerns voiced by groups opposed to the technology, and thus focus on the DNA of the transgene and its accompanying vector sequences, and any possible changes in the DNA around the transgene-insertion site, rather than on the trait itself. In consequence, the cost of regulation can run into the tens of millions of dollars per transgenic event. As such, the regulatory environment is actively preventing the marketing of dozens of transgenic crops, while contributing little, if anything, to public and environmental safety.

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Whether this DNA-centric regulation is warranted depends on the extent of DNA-based changes that differ between the engineering process and traditional plant breeding. The prevailing wisdom has been that plant breeding primarily depended on pre-existing variation, and thus need not cause novel DNA changes. Furthermore, the nature and extent of the DNA-level variation within a crop have been poorly quantified until now, although there have been indications in the literature that the plant-breeding process itself is mutagenic, that plant genomes are fluid and dynamic, and that there is a large amount of DNA-level variation.

Rasmussen and Phillips (1997) provided one of the first insights that the plant-breeding process is mutagenic when they concluded that barley breeders had achieved more progress from breeding and selection than could be explained by the amount of genetic variation originally present in the parents.

Are DNA Insertions Dangerous?

> *Traditional breeding is based on sexual reproduction between like organisms. The transferred genes are similar to genes in the cell they join.... In contrast, bioengineers isolate a gene from one type of organism and splice it haphazardly into the DNA of a dissimilar species, disrupting its natural sequence.* —Alliance for Biointegrity (http://www.bio-integrity.org/health-risks/ health-risks-ge-foods.htm)

It has long been known that DNA content can change during tissue culture, in the neighborhood of 10% per culture cycle (*e.g.*, De Paepe *et al.*, 1982). More recently, retrotransposon amplification has been implicated in tissue-culture-induced DNA changes (Jiang *et al.*, 2003).

Yet, DNA content changes in the absence of tissue culture. The literature contains many suggestions that plant genomes are highly variable. One early indication was the discovery that maize inbreds differ in the number of rDNA copies, ranging from a low of 5,000 in "W23" to 23,000 copies in "Illinois Reverse High Protein" (Phillips, 1978). Total DNA content varies also within crop varieties. For example, soybean genotypes differ from each other by as much as 12% in DNA content (Graham *et al.,* 1994). For red pepper, the difference goes up to 25%, (Mukherjee and Sharma, 1990) and for maize, 42% (Rayburn *et al.*, 1989)! It is clear from these results that plants can endure substantial changes to their DNA without ill effect. In the case of soybean, the 12% DNA is equivalent to almost 106 million bp. Hence, an extra 322 bp of vector sequences in something like Roundup Ready© soybean cannot make any significant difference.

Furthermore, it must be emphasized that these changes in DNA content do not necessarily represent ancient events, but rather are the consequence of modern breeding attempts. The previously mentioned case of variation in soybean DNA amount is probably derived from adaptations to growing seasons at different latitudes (Graham *et al.*, 1994); a similar relationship is found between the length of the growing season and the DNA content of maize (Bullock and Rayburn, 1991).

It is possible for DNA content to change within one generation. The most extreme example described is that of genotypes of flax that have heritable changes in plant size depending on the fertility of the soil (Durrant, 1962). These changes are caused by loss (up to 6%) or gain (up to 10%) of DNA content in the weeks following seed germination (Evans *et al.*, 1966). Smaller changes, unaccompanied by dramatic differences in the phenotype, possibly occur all the time but go undetected. For example, DNA content in tall fescue differs between plants germinated at 10°C rather than 30°C (Ceccarelli *et al.*, 1997), and reflects gain or loss of ~30% in copy number of different retrotransposons.

The major component that accounts for variability in genome size is the presence of retrotransposon elements, which are a major constituent of plant genomes (Bennetzen, 1998). Again, the question remains whether retrotransposon movement took place in the ancient past or continues on to the present. Biologically, it would be difficult to explain why retrotransposition was once common, then came to a stop. In fact, the presence of retrotransposon sequences in expressed sequence tag (EST) databases (Kuhl *et al.*, 2004; Neumann, *et al.,* 2003; Echenique *et al.,* 2002) suggests that some retrotransposons are active to this day.

Rapid genomic change is also evident upon polyploidization. DNA segments have been shown to appear and disappear within a generation following hybrid formation in *Brassica* (Song *et al.,* 1995), wheat (Liu *et al.*, 1998 a, b), tobacco (Skalická *et al.*, 2005) and arabidopsis (Pontes *et al.*, 2004; Madlung *et al.,* 2005).

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Collectively, these data strongly imply that plant genomes are quite able to endure insertions and excisions of DNA without ill effects. It cannot be concluded that "disruption of natural sequences" is dangerous.

What About Insertional Mutagenesis?

> *A foreign gene could, for example, be inserted in the middle of an existing gene that instructs a plant to shut off production of a toxin in its fruit. The foreign gene could disrupt the functioning of this existing gene, causing the plant to produce abnormal levels of the toxin in its fruit. This phenomenon is known as "insertional mutagenesis"—unpredictable changes resulting from the position in which a new gene is inserted. — Rachel's Environment & Health News* (http://www. rachel. org/bulletin/bulletin.cfm?Issue_ID=1931&bulletin_ID=48)

> *In most cases of plant modification, DNA insertion takes place at random, unpredictable loci. Such random insertion may lead to unintentional changes in gene expression.* — OECD Report of Task Force for the Safety of Novel Foods and Feeds (2000) [C(2000)86/ADD1]

Insertional mutagenesis differs from the previous topic in that the new DNA inserts itself into another gene or its regulatory sequences, rather than into the intergenic space. To evaluate the safety of insertional mutagenesis, it must be placed in context of transposable elements jumping in and out of genes, where they "can alter gene expression or serve as sites of chromosome breakage or rearrangement," (Wessler, 2001) just like transgenes, and usually without ill effects to the plants or those who consume them.

It must be noted that all crop plants go through a period of field trials before being released commercially. These trials ensure that no unexpected or undesirable effects from the breeding process—conventional or engineered—are present in the final product.

Is Horizontal Gene Transfer Unique to Transgenics?

> *Unlike traditional crop or animal breeding, genetic engineering enables scientists to cross genes from bacteria, viruses, and even humans into plants and animals. Never before have scientists been able to break the species barrier.* — The True Food Network (http://www.truefoodnow.org/ home_whatis.html)

Actually, plant breeders have been transferring genes between related species and related genera for decades. However, it is true that scientists had not crossed the species barrier in terms of gene transfer between kingdoms until the advent of genetic engineering technology. Nevertheless, it must be acknowledged that DNA from unrelated species is transferred and incorporated into plant genomes. For example, plantain bananas contain the entire genome of the banana streak virus, rice contains DNA from the rice tungro bacilliform virus, and tomato has DNA from the tobacco vein clearing virus (Harper *et al.*, 2002). In fact, these authors concluded the following: "It appears that integration of viral sequences is widespread in the plant kingdom and has been occurring for a long period of time." Genes from the bacterium, *Agrobacterium rhizogenes*, have been found incorporated into the genome of some tobacco species (Aoki and Syono, 1999; Ashby *et al.*, 1997), while DNA from unrelated higher plants has been found to be transferred between their mitochondria, and, from there, to their nuclei (Bergthorsson *et al.*, 2003, 2004).

The true extent of horizontal gene transfer will become clear as more plant genomes are sequenced. In the interim, it is fair to say that, although not a common phenomenon, horizontal gene transfer does take place, at least on an evolutionary time scale, and does not appear to pose any hazards to recipient plants.

The Impact of New Genes in a Genome

> *Gene expression is subject to a regulatory network of a complexity that is only just being realized.*

> *[Genetic engineering] assumes that genes act as isolated units within a system. This is simply not true....Genes inserted at random into the genome means* [sic] *are outside of these regulatory control—they are unregulated. GE goes against the current understanding of the complex nature of the genome.*
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> *…the often forcible insertion of DNA into a tightly controlled genetic regulatory network is likely to produce unintended effects.* —Greenpeace (http://www.greenpeace.org/international/campaigns/genetic-engineering/failings-of-ge)

The new argument being made is that genes are controlled by a regulatory expression web in which no gene is independent. A new gene or a gene in the wrong place can upset this regulatory web. Yet, as discussed previously, genes and DNA sequences move into and between chromosomes. As additional examples, genes are known to have moved from the chloroplast to the nucleus (Cummings *et al.*, 2003). *In situ* fluorescent hybridization has shown how DNA elements move from one genome to another in a tetraploid wheat (Belyayev *et al.,* 2000).

Furthermore, this "new" interpretation that gene expression is regulated by a fragile network of interdependent genes is based on the traditional concept that all members of the same species have the same genes in the same location. However, sequencing homologous DNA sequences from various maize inbreds is revealing a different reality: different individuals within the same species do not even have to have the same number of genes! Fu and Dooner (2002) first discovered this phenomenon. Since then, the finding has been extended to other maize sequences (Brunner *et al.*, 2005; Song and Messing, 2003). In hindsight, this result is not altogether surprising, as it has been known for years that cytoplasmic male sterility in a variety of plants results from the creation of novel genes in the mitochondrion, along with novel fertility restorer genes in the nucleus (Schnable and Wise, 1998). Nevertheless, the point is that to the extent to which these regulatory networks exist, they are sufficiently robust so as not to be affected significantly by the presence/absence or location of single genes or DNA sequences.

Antibiotic Resistance Genes

> *Scientists are concerned that by flooding the environment with antibiotic tolerance genes, these genes will be taken up by disease-causing bacteria, which would then become uncontrollable by antibiotics.* —http://www.sare.org/sanet-mg/archives/html-home/19-html/0256.html

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The concern that resistance can be passed from a transgenic plant to a pathogen is misguided.

The concern that resistance can be passed from a transgenic plant to a pathogen is misguided. As background, transgenic plants can have two antibiotic resistance (AR) genes in them. One is used to distinguish transgenic from non-transgenic cells. These AR genes are modified to be expressed by plant cells, but not by bacteria. Even if they were expressed by bacteria, it turns out that the specific AR genes used during the genetic engineering process of crop plants are already ubiquitous. The gene for kanamycin resistance is an example. It has been calculated that the average human has 1,000,000,000,000 kanamycin-resistant bacteria living in her/his gut, and eats an additional 1.2 million such bacteria each day (Flavell *et al.,* 1992). The bottom line is that while it might be remotely possible to transfer an AR gene from a plant to a pathogen, it is infinitely more probable that such a transfer would take place from the multitudes of AR genes already present in the environment.

The second type of AR gene used is associated with gene-gun-mediated transformation to keep the plasmid in the bacterium, usually by conferring resistance to ampicillin or tetracycline. In contrast to the plant markers, these are expressed in bacteria. However, they are also ubiquitous. For example, 90% of stool samples from Mexico contain ampicillin-resistant *E. coli* (Calva *et al.*, 1996). Fifty percent of the *E. coli* from the average person in France are ampicillin resistant. Using the estimate of 500 g/feces/person/day, and the presence of between 1 million and 1 billion *E. coli* cells per g of feces, half of which are resistant to ampicillin, each French person liberates somewhere between 250 million to 2.5 billion copies of the ampicillin-resistance gene each day (Berche, 1998). Genes for tetracycline resistance are present in many soils. For example, a recent study from Denmark found tetracycline-resistance genes in 10% to 80% of sampled farm soils, and in all samples after enrichment with manure, using a detection limit of 10^2 to 10^3 copies of the gene per g of soil (Agerso *et al.,* 2004). Finally, 6% of wild rodent feces contain tetracycline-resistant bacteria (Hauschild *et al.* 2003).

As of now, transfer of an AR gene from a plant to a pathogen has not been documented under real-world conditions. Nevertheless, the point is that if it were to happen it would not matter, due to the number of resistance genes already in the environment. Thus, efforts to produce engineered plants without AR genes unnecessarily complicates the engineering process, without gaining any safety benefits.

Regulatory Implications

The basis for a phenotypic-trait-based regulatory system, as opposed to a DNA-based system, has been laid out in a series of papers (Strauss, 2003a, b; Bradford *et al.*, 2005). The premise is that examining changes at the DNA level will most likely result in unnecessary expense and not contribute towards environmental or health safety.

Risk Categories

The first step in moving towards a trait-based regulatory system is recognizing that transgenes can be placed into low-, medium-, or high-risk categories based on their function.

Low Risk

The vast majority of transgenes would probably be in this category, and require little or even no oversight. Examples of transgenic crops in this category would include those:

- When the transgenic trait is functionally equivalent to one obtained by breeding
- When the transgenic trait is "domesticating," that is, it lessens fitness in the wild
- No novel biochemical or enzymatic functions are imparted.

Medium Risk

- Plant-made pharmaceuticals/plant-made industrial products (PMPs/PMIPs) of low animal/environmental toxicity
- Resistance traits that require stewardship for their protection.

High Risk

- PMPs/PMIPs with documented ability to cause harm in the environment or upon ingestion
- Plants used for bioremediation that accumulate heavy metals or other toxins

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Avoid Event-Specific Regulation

Once a trait produced by a transgene is deemed to be innocuous, additional transgenics produced with the same transgene should not have to go through the entire regulatory process, if at all, particularly if the same transgene is introduced into the same crop. Putatively, *de novo* regulation of each transgenic event precludes unintended effects between the transgene and the recipient genetic background. Yet, the current regulatory climate is such that once a given transgenic event is approved, it in turn is backcrossed into hundreds if not thousands of different varieties, thus virtually ensuring the transgene will end up in various genetic backgrounds anyway. If anything, the widespread use of transgenes backcrossed into different genetic backgrounds is living proof that background effects, if they exist, are not important enough to regulate.

Adventitious Presence

It has long been recognized that zero tolerance is virtually impossible to achieve, be it in food products or in seed. Nevertheless, the continued and stringent regulation of transgenic products has given the public the distinct impression that these are dangerous, to

the point that tolerances for the adventitious presence of transgenes and their products are far more strict than the tolerances for the presence of contaminants. For example, certified seed is allowed to have a low level of foreign matter and seeds from other varieties or even other crops, and some types of weeds. A case in point: certified canola seed may legally have two seeds from other crops per 50 g. It can also have fifty weed seeds per 50 g, though none can be of a noxious weed, and only two can be of objectionable weeds. Also, there can be ninety diseased seeds per lb. Furthermore, one of every 500 canola plants in the seed field can be an off type or from another variety. It is unreasonable to expect transgenic seed to be present at lower levels than within these tolerances.

Likewise, the Food and Drug Administration/Office of Regulatory Affairs (FDA/ORA) filth standards allow limited amounts of insect parts and rodent waste in food. As examples see CPG 7104.02, Sec 578.200 and CPG 7114.29, Sec 585.890 for cornmeal (permits less than one whole insect, or fewer than fifty insect fragments, or fewer than two rodent hairs, or less than one fragment of rodent excreta per 50 g) and for tomato paste (permits twenty-nine fly eggs, or fourteen fly eggs plus on maggot, or fewer than two maggots per 100 g), respectively. As another example, under the *Codex Alimenatarius* (3.2.2.1) international standards, white rice can have impurities of animal origin (including dead insects) of 0.1% m/m maximum. There is something totally irrational about allowing 0.1% dead insects in white rice, but panicking if trace amounts of a transgenic protein were to appear in the same rice.

The adventitious presence of transgenes and their products should not trigger regulatory action as long as they are not present in quantities that exceed the standards currently in place for certified seed, for the FDA/ORA filth standards, or for the Codex Alimentarius.

The adventitious presence of transgenes and their products should not trigger regulatory action as long as they are not present in quantities that exceed the standards currently in place for certified seed, for the FDA/ORA filth standards, or for the *Codex Alimentarius.* Another criterion that may be used is that the adventitious presence of transgenes and their products fits within FDA recommendations as to whether trace ingredients must be labeled. The following is from http://www.cfsan.fda.gov/~dms/flg-4.html, on the need to label:

> *…depends on whether the trace ingredient is present in a significant amount and has a function in the finished food. If a substance is an incidental additive and has no function or technical effect in the finished product, then it need not be declared on the label.*

Thus, if the adventitious presence would not trigger the FDA-labeling requirement, such adventitious presence should not be regulated. Under these criteria, low-level presence of transgenes and their products in foods should be exempted from regulations. In addition, there should be allowances for adventitious presence that are based on risks of specific classes of genes, and not on method (GE or not), with the classes discussed above. These should include the unlimited presence of specific selectable marker and reporter genes, and vector DNA sequences.

Additional Issues

Currently, genetically engineered *Arabidopsis* spp. are exempt from interstate movement restrictions under 7 CFR part 340, as are *E. coli* K-12, *Saccharomyces cerevisiae* and *Bacillus subtilis*. Note that these same organisms are currently regulatory exempt from NIH guidelines as per Appendix C, while *Arabidopsis* is exempt provided that it does not meet the criteria in Section III-E-2-b or other sections of the NIH Guidelines:

> *Examples of such experiments are those involving recombinant DNA-modified plants that are not noxious weeds or that cannot interbreed with noxious weeds in the immediate geographic area, and experiments involving whole plants and recombinant DNA-modified non-exotic microorganisms that have no recognized potential for rapid and widespread dissemination or for serious detrimental impact on managed or natural ecosystems (*e.g., Rhizobium *spp. and* Agrobacterium *spp.).*

The key here is that NIH views *Agrobacterium* as low risk, whereas APHIS regulates interstate transport of all *Agrobacterium* strains, even when they have been disarmed and are no longer pathogenic. Accordingly, all interstate movement restrictions of transgenic organisms that are of low to moderate risk as defined above, or that could not establish in the environment without substantial human aid, need to be lifted. This would greatly facilitate research and breeding with GE materials, and regulatory effort could then be focused on the more important issue of environmental releases, not contained shipments. Exemptions from regulation should include:

- All disarmed *Agrobacterium* strains not containing T-DNA
- All low-risk transgenic plants as defined above (as seed, in soil, or *in vitro*).

Summary

Plant genomes are variable and dynamic, constantly changing in response to breeding efforts and even to environmental conditions. They are buffered against the change that

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Ultimately, it is the trait imparted by the transgene that matters, and as such, it is the trait that should be the focus of regulatory efforts, should these be warranted.

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small additions or deletions of DNA can cause. They are buffered against differences in genic content, which probably explains why polyploidy is prevalent in higher plants.

Against this background, it is ludicrous to treat transgenes and their associated DNA changes as inherently dangerous. Ultimately, it is the trait imparted by the transgene that matters, and as such, it is the trait that should be the focus of regulatory efforts, should these be warranted. For most traits, their risk to health and the environment is low enough as to preclude the need for regulatory oversight.

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