nature biotechnology

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They should be addressed to:
Correspondence
Nature Biotechnology
345 Park Avenue South
New York, NY 10010-1707, USA
or sent by e-mail to biotech@natureny.com
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Beyond gene containment

To the editor:

We are writing to you on behalf of the UK statutory conservation agencies, which welcome your editorial "Going with the flow" (*Nat. Biotechnol.* **20**, 527, 2002).

For several years, we have been advocating gene-containment strategies to add to the environmental safety of novel crops. Note that we refer to "novel" crops and not to genetically modified (GM) crops, as we agree with your view that this is not an issue that applies solely to transgenic crops. However, we believe it is necessary to consider a wider context than gene flow *per se* to avoid placing too much reliance on containment technology. It is entirely possible that, rather than seeing gene containment as an added safety mechanism, some biotechnologists may see the technology as a "green light" to introduce potentially risky genetic traits that otherwise might be rejected by regulatory authorities. This regulatory problem needs to be resolved.

Perhaps the most obvious and simple gene-containment strategy, often overlooked in these debates, is choosing the right plant for transformation. There seems to be a trend toward transforming food plants (especially corn and oilseeds) for pharmaceutical and industrial feedstock traits that, even with effective gene containment, will cause public concern over the adulteration of basic foods. Some of these plants can also outcross to wild ancestors. If we want to produce "designer" molecules from agriculture, why not choose crops that have no sexually compatible relatives in the intended market area? By choosing the right plant, the development of gene-containment mechanisms may be unnecessary—evolution and plant breeding have already done the job.

It is also important to consider just how effective gene-containment strategies could be. We agree with you that the potential of these technologies should be researched as thoroughly as possible, but this must include rigorous and transparent determination of their fallibility before they are used as mechanisms to contain novel traits. Of the molecular-containment technologies currently being researched (*Nat. Biotechnol.* **20**, 581, 2002), chloroplast transformation is one of the most promising. Although it is highly effective in some model plant species, it is not very effective in other plants, including several crops exhibiting a degree of paternal inheritance[1]. The potential "leakiness" of this technology also applies to others, such as male sterilization.

Assuming that gene-containment strategies become a practical option, it may be that different containment technologies will need to be tailored to individual crops. It is likely that at least two strategies with entirely different mechanisms may be necessary to provide sufficient containment in any one crop. In the United Kingdom, we call this a "belt and braces" approach. If adopted, it could help to inspire confidence in politicians and the public. After all, such an approach has been adopted by many other industries, such as electrical engineering and car design, where backup safety precautions are standardly installed, even when they are not scientifically justified or required by law.

We see the potential for cross-pollination and gene stacking in crops and/or wild relatives as a difficult and long-term regulatory challenge in the commercial release of novel crops. When one novel crop gets regulatory approval, it may be followed by further release of the same crop possessing different and sometimes multiple novel traits. We have seen this in the large increase in genetic transformations of corn and oilseeds globally. The incidence of uncontrolled gene stacking and the consequent potential impact on agriculture and ecology are ill understood because very little research is being done in this area. Because of lack of data, global regulatory systems controlling novel crop release fall short of proper consideration of the environmental impacts of gene stacking. Given the lack of public and private investment in biosafety research generally (*Nat. Biotechnol.* **20**, 542, 2002), it is difficult to see how we can properly assess the cumulative impact on the environment of hybrid plants resulting from the release of different novel varieties of the same crop, *let alone* hybrids between and within wild plant–crop complexes.

In light of the continuing controversy surrounding GM crops in the United Kingdom and other European countries, as well as public mistrust of scientists and the agricultural industry, there is every reason to adopt precautionary techniques that can add to agricultural sustainability and safety in developing novel crops. If industry continues to ignore the gene-flow issue, the public may eventually turn their backs on the use of novel gene technology in agriculture.

Brian Johnson and Rebecca Dallimore,
Biotechnology Advisory Unit
English Nature
Taunton, UK
(Rebecca.dallimore@English-Nature.Org.UK)

1. Advisory Committee on Releases to the Environment: Sub-group on Best Practice in GM Crop Design. *Guidance on Principles of Best Practice in the Design of Genetically Modified Plants.* (Department for the Environment, Food & Rural Affairs, London, 2001).

QC in antisense oligo synthesis

To the editor:

Interest in oligonucleotide antisense therapeutics has regained momentum[1,2]. One antisense therapeutic, Vitravene, has been approved, 12 are in clinical trials[1], and others are in various planning stages[3]. High-quality chemical synthesis of antisense oligonucleotides via nucleobase and sugar-protected phosphoramidites is crucial to the expectations of low toxicity, reduced side effects, and low costs[2]. However, neither the coupling reaction producing the growing polymer chain nor the subsequent deprotection of the full-length oligonucleotide occurs with 100% efficiency[4]. Thus, quality and regulatory concerns about antisense therapeutics have been expressed by scientists at the Food and Drug Administration (FDA; Rockville, MD)[5].

Incomplete deprotection of nucleoside-reactive groups could be responsible for the unexplained results observed in the early *in vitro* and cellular stages of drug discovery[2]. It could also be responsible for immunological responses seen at high doses in animal models and clinical trials[2] and thus contribute to erroneous conclusions about