Commentary

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A different perspective on GM food

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As a cell biologist, I am very discouraged by the nature of the ongoing "debate" on the introduction of genetically modified (GM) plants into the marketplace. This discussion has usually pitted irrational emotional arguments against the apparently rational notion that genetic engineering is just like traditional plant breeding, only more specific. In particular, I believe that insufficient attention has been paid to three important issues: first, introduction of the same gene into two different types of cells can produce two very distinct protein molecules; second, the introduction of any gene, whether from a different or the same species, usually significantly changes overall gene expression and therefore the phenotype of the recipient cell; and third, enzymatic pathways introduced to synthesize small molecules, such as vitamins, could interact with endogenous pathways to produce novel molecules. The potential consequence of all of these perturbations could be the biosynthesis of molecules that are toxic, allergenic, or carcinogenic. And there is no *a priori* way of predicting the outcome. In what follows I outline these concerns and argue that GM food is not a safe option, given our current lack of understanding of the consequences of recombinant technology.

The biological activity of a protein can be modified by gene splicing, which alters the primary amino acid sequence, and by the post-translational attachment of such moieties as phosphate, sulfate, sugars, or lipids. The nature of these modifications is markedly dependent upon the cell type in which the protein is expressed. For example, if the β-amyloid precursor protein, which is involved in Alzheimer's disease, is expressed in glial cells, it contains covalently attached chondroitin sulfate; but when it is expressed in brain nerve cells the protein contains a much simpler sugar[1]. This is because each cell type expresses a unique repertoire of enzymes capable of modifying protein structure by mRNA splicing or at the post-translational level. In the case of the β-amyloid precursor protein, its adhesive properties are altered by the attachment of different carbohydrates[2]. With our current state of knowledge, however, there is no way of predicting either the modifications or their biological effects. Therefore, a toxin that is harmless to humans when made in bacteria could be modified by plant cells in many ways, some of which might be harmful.

My second concern is the potential for the introduction of a foreign gene to either evoke the synthesis of toxic, carcinogenic, teratogenic, or allergenic compounds, or downregulate the synthesis of a beneficial plant molecule. Introduction of one gene usually alters the gene expression pattern of the whole cell, and typically each cell type of the organism will respond differently. One example involves the transfection of a receptor gene into human cells. In this case, the protein was a closely related isoform of an endogenously expressed gene[3]. Monitoring the pattern of gene expression using microarray technology showed that mRNA levels for 5% of the genes were significantly upregulated or downregulated. Recent studies in transgenic plants showed that the over-expression of a gene involved in pectin synthesis had no effect in tobacco, but caused major structural changes and premature leaf shedding in apple trees[4]. Although these sorts of unpredicted changes in gene expression and function are frequently observed, they have received very little attention. Furthermore, they are not unexpected. The maintenance of a specific cell phenotype

involves a very precise balancing act of gene regulation, and any perturbation might be expected to change the overall patterns of gene expression. The problem, as with secondary modifications, is that there is currently no way to predict the resultant changes in protein synthesis.

Third, the introduction of genes for all or part of a new enzymatic pathway into plants could lead to the synthesis of unexpected or even totally novel products through an interaction with endogenous pathways. Some of these products could be toxic. For example, retinoic acid (vitamin A) and its derivatives are used in many signaling events that control mammalian development[5]. As these compounds have effects at ultra-low concentrations, a GM plant making vitamin A might also produce retinoic acid derivatives, which act as agonists or antagonists in these pathways, resulting in direct toxicity or abnormal embryonic development. A relevant example is a genetic manipulation carried out in bacteria during the 1980s to increase the yield of tryptophan for use as a nutritional supplement. The resultant product caused a novel illness that was highly correlated with the aberrant appearance of specific trace contaminants[6].

Given that GM plants will sometimes produce different amounts of proteins, and perhaps totally new proteins, as compared with the parental species, what are the possible results? A worst-case scenario would be that an introduced bacterial toxin is modified to make it toxic to humans. Prompt toxicity might be rapidly detected once the product entered the marketplace if it caused a unique disease, and if the food were labeled for traceability, as were the GM batches of tryptophan. However, cancer or other common diseases with delayed onset would take decades to detect, and might never be traced to their cause. Conversely, plant flavonoids and related molecules have great health benefits[7], and there is evidence that these can be depleted in GM crops[8].

If the above concerns are valid, what can be done to address them? Secondary modifications could be assayed by monitoring of the introduced gene product by mass spectroscopy; changes in gene expression could be assayed by DNA chips; and metabolically active molecules could be measured biochemically. The problem is, of course, that unless we know exactly what to look for, we are likely to miss the relevant changes. To me, the only reasonable solution is to require that all GM plant products destined for human consumption be tested for long-term toxicity and carcinogenicity before being brought to market. These safety criteria must be met for many chemicals and all drugs, and the magnitude of harm caused by a widely consumed toxic food could well be much greater than that from any single drug. However, even extensive animal testing might not detect the consequences of deficiencies in beneficial plant products. As GM crops offer potential benefits, it would be in the industry's best interest to more thoroughly examine these products before continuing with their introduction into the food supply.

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Divergent perspectives on GM food - Letter 2

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To the editor

I have several questions about and comments on David Schubert's commentary "A different perspective on GM food" published in the October issue (*Nat. Biotechnol.* **20**, 969; 2002). Schubert raises three scenarios in which agricultural biotechnology could lead to the "biosynthesis of molecules that are toxic, allergenic, or carcinogenic." These include differential post-translational protein processing, unexpected changes in gene expression, and disruption of endogenous enzymatic pathways.

Schubert writes that the only "reasonable solution is to require that all GM plant products destined for human consumption be tested for long-term toxicity and carcinogenicity before being brought to market. These safety criteria must be met for many chemicals and all drugs."

My first question is why these concerns don't apply equally to new crop varieties that are developed through intensive radiation or chemical mutagenesis? All of these unknowns are as relevant to mutagenesis-derived varieties, or to varieties that are created by wide-crosses, as they are to crops developed through recombinant genetic technologies. It is also worth noting that current US regulatory rules already account for instances where the genetic modification results in a significant change in the composition of the foodstuff.

The issue of allergenicity is tricky because there is currently a double standard. Although there appears to be a zero-tolerance policy for novel foods, allergenic foodstuffs that have been on the market for decades are permitted. Yes, they require clear labeling, but they are not banned or removed from the market. Peanuts, kiwi, corn, wheat, and many other foods are allergenic to some people, sometimes lethally so.

In fact, biotechnology is a powerful tool to reduce these natural risks as well as any potential allergy risks in novel genetically modified (GM) foods. This has now been clearly demonstrated by the recent removal of the major allergenic protein from soybeans. Our predictive capabilities and knowledge of what makes specific proteins allergenic is increasing monthly. Our regulatory authorities already take such risks into full account, as demonstrated by the Starlink episode.

Human food approval of Starlink corn was rejected based on purely hypothetical risks. This example proves the already heavy precautionary stance of current biotechnology food regulations.

As to Schubert's suggestion for long-term safety testing of novel biotechnology foods: there are fundamental differences between foodstuffs and products like pharmaceuticals. First, it is simply not possible to conduct the kind of "high-dose" carcinogenicity testing (or whatever else Schubert means by "long-term toxicity" testing) on food products, which is conducted for individual chemicals or pharmaceuticals. To do so requires high-dose testing, and consuming high doses of single foodstuffs of-ten significantly affects health because of a fundamental lack of balance in the diet. Second, if a food is toxic, long-term testing isn't necessary. Short-term (that is, acute toxicity) testing will be fully sufficient.

Moreover, with the current debate about acrylamide formation in cooked foods and the presence of natural carcinogens in our foods, a strict implementation of Schubert's testing scenario would result in most of our totally natural foodstuffs being pulled from the market. What would be the regulatory enforcement standard for carcinogens or "long-term toxicity" in novel foods? Worse than a cup of coffee? Worse than lettuce, fried bacon, or mushrooms? All contain natural carcinogens and chemicals that are toxic at higher doses.

Finally, Schubert contends that the Shawadenko tryptophan toxicity episode was the result of genetic engineering of the bacteria. Having researched this topic considerably, I was under the strong impression that the toxic contaminant in the dietary supplements was found to result from the elimination of a key purification step from product processing, rather than from the bacteria having been genetically engineered.

See Divergent perspectives on GM food by Parrott *et al.* and the Reply to 'Divergent perspectives on GM food' by D. Schubert.

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Divergent perspectives on GM food

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To the editor

In his commentary "A different perspective on GM food" in the October issue (*Nat. Biotechnol.* **20**, 969, 2002), David Schubert identifies three hazards arising from the introduction of genes into plants and concludes that "GM food is not a safe option." According to Schubert, an introduced gene may first, produce different proteins in different cell types; second, produce proteins that will react with other substances in a cell to result in "the biosynthesis of molecules that are toxic, allergenic, or carcinogenic"; or third, result in the formation of a new biochemical pathway giving rise to novel or unexpected products of physiological consequence. The fatal flaw in this argument is that each of these three scenarios raised can and do occur in nature during the course of the random "natural" gene mutations and rearrangements that drive evolution. Nevertheless, Schubert dismisses "the apparently rational notion that genetic engineering is just like traditional plant breeding, only more specific." He concludes: "As GM crops offer potential benefits, it would be in the industry's best interest to more thoroughly examine these products before continuing with their introduction into the food supply."

Schubert must be aware that many other scientists have gone before him in considering these same issues. The potential hazards of any new technology must be assessed as Schubert suggests, and that is exactly why the scientific and regulatory establishments in many countries have put in place comprehensive pre-market safety evaluation processes before permitting a new product of biotechnology to enter the marketplace. The process for safety assessment of biotechnology products was established by some of the world's leading scientists through WHO/FAO/CODEX and has been confirmed repeatedly in published studies and reports by numerous regulatory and scientific authorities globally.

First, it should be noted that crops produced through biotechnology are subjected to a highly selective screening process that is unlikely to permit unintended or unexpected variation. To satisfy the farmer, the plant must grow and perform in the field as well as or better than its conventional counterpart; furthermore, the new variety will be subjected to a wide array of compositional and functional tests. Only those plants that meet the most stringent performance and safety criteria will advance to the regulators' desks where the results of the safety studies will be independently assessed (see http://64.26.172.90/agbios/dbase.php for a summary of assessments). The net result is that safety assessments for biotechnology crops do not rely on *a priori* predictions, such as those offered by Schubert, but instead focus on careful analyses of plants. The system for ensuring the safety of such crops is "evidence-based" not "prediction-based."

The battery of scientific tests conducted on all biotechnology crops is designed to detect unpredicted effects from all kinds of sources, including alternative splicing of mRNAs and post-translational processing of the target protein, and any other unexpected impacts on plant metabolism that might occur. It is instructive to follow one of Schubert's arguments to its logical conclusion. He suggests that genes may produce different proteins in different cells. Of course, the gene must express the intended protein in the predicted manner or the plant would not display the desired phenotype or trait and would therefore be discarded from further consideration by the developer. The protein produced in the new host is subjected to extensive biochemical characterization to confirm that the protein produced is the one and only one intended. Additional tests include acute toxicity and allergenicity evaluations, extensive agronomic, performance and yield analyses, molecular and biochemical characterization of the expressed protein to assure specificity, compositional analyses of key metabolites and nutrients, and animal nutrition and feed-performance studies.

Schubert mentions the reported depletion in isoflavone content in genetically modified (GM) soybean as a demonstration of unintended changes that might occur. Setting aside the fact that the changes he cites were in fact detected, these variations, measured in different varieties of soybeans produced in different growing seasons, fall precisely within the range of concentrations of isoflavones normally found in soybean varieties[1]. We are also told that toxic metabolites were created in "GM batches of tryptophan." This allegation is often found in "anti-GM" publications; however, no peer-reviewed published research points to an association of GM technology with the suspected toxic impurities. Instead, publications demonstrate that the increase in the impurity(s) resulted from a change in the purification process. And, finally, some have attributed toxic effects, such as eosinophilia-myalgia syndrome, to the consumption of unprecedented high doses of l-tryptophan *per se*[2]. When Schubert states that "a GM plant making vitamin A might also produce retinoic acid derivatives" that could result "in direct toxicity or abnormal embryonic development," he ignores the fact that "golden rice" was engineered to produce vitamin A precursors (as opposed to the vitamin itself) and that all green plants synthesize its precursors. Thus, we are offered hypotheses for which there is no confirmatory evidence and evidence that is without merit.

The real issue, however, is not one of scant or non-existent evidence, but of not considering the genetic realities that accompany all methods of plant breeding, whether conventional or biotechnological. We do not take issue with Schubert's basic contention that unintended genetic and metabolic events can take place. The reality is that "unintentional consequences" are much more likely to occur in nature than in biotechnology because nature relies on the unintentional consequences of blind random genetic mutation and rearrangement to produce adaptive phenotypic results, whereas GM technology employs precise, specific, and rationally designed genetic modification toward a specific engineering goal.

A recent paper illustrates the point. Fu and Dooner[3] report the sequence of approximately 100 kb around the naturally selected *bz* mutant gene in maize, obtained from two different maize varieties. Alignment shows that one variety possesses four genes that are missing from the other. The authors offered the speculation that hybrid vigor may result when two parents complement each other's missing genes. In the world of plant breeding, new genes and different alleles are constantly being shuffled and reshuffled in an endless array of combinations. In the end, traditional breeding practices all have the same, if not greater, potential ability as a transgene to produce different proteins in different cell types, or produce proteins that will react with other substances in a cell to result in "the biosynthesis of molecules that are toxic, allergenic, or carcinogenic."

Good scientists go astray when they leave their area of expertise to offer opinion when they have not studied the literature, when they selectively ignore information, or when they let their politics

and beliefs interfere with the objectivity of their science. Such opinions do little to encourage an informed debate about GM crops, and it is inevitable that Schubert's arguments will be cited as having been published in *Nature Biotechnology*.

See Divergent perspectives on GM food - Letter 2 by A. Avery and the Reply to 'Divergent perspectives on GM food' by D. Schubert.

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Competing interests

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To the editor

In August, more than 30 scientists and the Center for Science in the Public Interest (CSPI) called on the editors of *Nature* journals to establish more robust policies for disclosing potentially biasing conflicts of interests among authors of scientific articles and quoted experts (http://www.cspinet.org/new/200308211.html).

One of the cases cited as an example of a *Nature* journal's failure to disclose corporate affiliations of authors was an exchange of correspondence in *Nature Biotechnology* (**21**, 1195−1197, 2002) concerning a commentary by David Schubert published in the October 2002 issue of the journal (*Nat. Biotechnol.* **21**, 969, 2002). While *Nature* journal policy at the time was to disclose competing interests only of authors of primary research papers, the failure to reveal industry ties in this correspondence contradicts the journal's aim of transparency and deprives readers of information that is highly relevant to the contentious debate over genetically modified (GM) foods.

David Schubert (who has received research and consulting funds from Genentech (S. San Francisco, CA, USA) and Agouron (La Jolla, CA, USA)) focused his commentary on the potential unanticipated effects of genetic engineering on the safety of GM foods. In December, *Nature Biotechnology* published a reply signed by 18 scientists disputing Schubert's arguments. At least 11 of these authors have close ties to companies that directly profit from the promotion of agricultural biotechnology.

For example, Roger Beachy, Director of the Danforth Plant Science Center (St. Louis, MO, USA),

has received substantial research funding from Monsanto (St. Louis, MO) and acts as a consultant to the United Soybean Board (Chesterfield, MO, USA) and Akkadix (Lafayette, IN, USA), an agricultural gene discovery company. The Danforth Center was launched with a $70 million pledge from Monsanto, which also donated the land for the center, a 40-acre tract adjacent to its St. Louis campus valued at $11.4 million; Bruce Chassy has received research grants from major food companies and has conducted seminars for Monsanto, Mills Labs (Minneapolis, MN, USA), Unilever (Gaithersburg, MD, USA), Genencor (S. San Francisco, CA, USA), Amgen (Thousand Oaks, CA, USA), Connaught Labs (now part of Aventis, Strasbourg, France) and Transgene (Strasbourg, France); Chris Lamb is a cofounder of and science advisor to Akkadix, which also funds the John Innes Centre (Norwich, UK), of which he is the director. Akkadix has also acquired exclusive rights to a gene discovery technology developed by signer Martin Yanofsky, who, with his colleague and fellow-signer Julian Schroeder, have exclusive consulting agreements with Akkadix. Charles Santerre was funded by Monsanto to study how training on food biotechnology can change consumer attitudes favorably toward GM foods. *Nature Biotechnology* disclosed none of these affiliations.

Where science and policy meet, debate necessarily transcends the boundaries of scientific disciplines. Thus, when considering controversial topics like GM foods, it is essential to disclose the financial interests that may play a role in these debates.

We do not believe that industry funding necessarily undermines the quality of research or biases the opinions of those who receive this financial support. However, there have been enough studies indicating a correlation between industry funding and opinions favoring industry interests to warrant heightened attention to this potential problem.

We believe that responsible scientific publication requires routine disclosure of the potentially biasing conflicts of interest of published authors. We urge *Nature* journals to extend their disclosure policy to include correspondence.

Editor's note:

Nature Biotechnology and other *Nature* journals are currently reviewing whether to expand our competing interests policy on research articles to other types of content, such as correspondence. We will include The Center for Science in the Public Interest's recommendations in our consideration.