

OPINION

Scientific perspectives on regulating the safety of genetically modified foods

Michael Gasson and Derek Burke

Regulation is often seen as the dull end of science. The recent storm over the introduction of genetically modified foods and the calls to regulate their consumption have had a negative effect on development of the science. Assuring the safety of genetically modified foods might raise questions where existing scientific data is limited and underline the need for further research.

Over the past few years, the introduction of genetically modified (GM) crops and GM foods into Europe has gone spectacularly wrong. Three objections have been raised against the genetically engineered crops: first, that the foods derived from them are unsafe to eat (FIG. 1); second, that their cultivation will harm the environment; and last, that there is something intrinsically wrong about the new technology, so much so that it should be rejected — root and branch. The first two concerns have been the business of regulatory committees, and are the focus of this article. The process of assessing the possible risk of genetic technology to health and to the environment has generated many scientific questions, which have promoted some interesting research. The third objection springs from a host of economic, political and ethical considerations and will not be discussed.

Concerns about possible risks to health caused by GM food — fuelled by the Pusztai report¹ that feeding GM potatoes to rats had a deleterious effect on their growth rate and immune function — are being increasingly brought into question by the strong scientific rejection of the validity of

the report (see link to the [Royal Society](#))², together with the fact that more and more US citizens eat GM soya without any detectable effect on their health. As the Organisation for Economic Cooperation and Development (OECD) Edinburgh Conference on “GM Food Safety: Facts, Uncertainties, and Assessment” stated in February 2000: “Many consumers eat GM foods. No significant adverse effects have yet been detected on human health”³. Indeed, two other groups have tested the original claim by feeding transgenic sweet peppers and tomatoes to rats⁴, and by feeding GM soya to mice and rats⁵, with no adverse effect. Nevertheless, concerns persist, and the current procedures for assess-



Figure 1 | “I hope there’s nothing genetically modified in this”.

Image provided by CartoonStock.

ing such risks have been questioned. These issues are discussed below.

In contrast to the concerns about the adverse effects of GM agriculture on human health, those surrounding the effect of GM technology on the environment are more diffuse and much more difficult to evaluate. They include issues such as the transfer of genes between related species, the production of SUPERWEEDS, the creation of new diseases or disease susceptibility, an increase in allergic reactions and the disruption of existing ecosystems (for a further discussion of these issues, see REF. 6).

Approaches to safety evaluation

A frequently raised objection to the current approach to regulating the consumption of novel foods is the limited reliance on experiments that monitor the effects of feeding whole foods, rather than their components, to animals. In this respect, the results of Pusztai’s experiments were hailed as an example of what might have been overlooked¹. There is a sound reason for not testing novel foods in the same way as pharmaceuticals or foreign chemicals (for example, flavourings or colourings) that are introduced into food. The conventional approach — feeding increasing amounts of a test substance to an animal until an adverse effect is observed — is limited by the sheer bulk of the food and, because whole foods contribute to nutrition, it is difficult to differentiate the negative effects of feeding large quantities of food from those caused by the novel technology. It is also difficult to justify killing large numbers of animals if the validity of the experimental approach is questionable.

The inherent difficulty of using conventional toxicology methods for the safety evaluation of novel foods was recognized over a decade ago, and new approaches have been developed under the guidance of the World Health Organisation (WHO), the OECD and the Food and Agriculture Organisation (FAO)^{3,7–9}. Their recommended approach is

Box 1 | Substantial equivalence

What is substantial equivalence?

- Substantial equivalence recognizes the fact that conventional foods have been eaten by many people over a long period of time and have an established and accepted level of safety.
- Genetic modification involves the introduction of a limited amount of change and substantial equivalence uses a comparative approach to reveal both intended and unintended differences between a genetically modified (GM) food and its conventional counterpart.
- This is achieved by the acquisition of a substantial body of phenotypic data, including agronomic traits and detailed chemical composition. Detailed chemical analyses are made of fat, proteins, solvent-extracted hydrophilic matter, fatty-acid and amino-acid profiles; micronutrients, antinutrients, crude fibre, ash and moisture contents as well as any known toxins or allergens. The Advisory Committee on Novel Foods and Processes (ACNFP) has provided guidance on the statistical validity and the effect of differing environmental conditions.
- Substantial equivalence is not in itself a safety evaluation and it is not intended to identify hazard. It reveals differences with respect to a conventional benchmark, which become the focus for detailed safety evaluation.

Improving substantial equivalence

- Greater consistency in comparative analysis is being sought through the preparation of OECD (Organisation for Economic Cooperation and Development) consensus documents for individual crop species, including soya bean, canola, potato and sugar beet¹⁴.
- Molecular-profiling techniques might provide a more holistic comparative analysis of conventional and GM foods¹⁵.
- Metabolic-profiling techniques can radically extend the breadth of compositional analysis, and post-genomic analytical techniques, such as DNA microarrays and total protein expression using proteomics, might be used in future.
- These new techniques need to be validated and the significance of any observed differences between conventional and GM foods needs to be considered against the very considerable background of natural variation caused by plant development, the environment and conventional breeding.

encompassed in the 'substantial equivalence' concept described in BOX 1. The use of substantial equivalence in safety evaluation has caused confusion, leading both to vigorous criticism¹⁰ of the method and to its equally vigorous support^{11–13}. Although the use of substantial equivalence has been effective so far, there is concern that it might not cope with future, more complex uses of GM technology.

Specific safety issues

The process of genetic modification. The term 'GM food' covers a diverse range of distinct gene-technology applications. These include the use of microbial and fungal cells as factories for the production of food-processing enzymes and food additives (TABLE 1). A good example is the use by the cheese industry of recombinant CALF CHYMOSIN, produced from GM strains of *Aspergillus niger*, *Kluveromyces lactis* or *Escherichia coli*. Food fermentative microorganisms, such as yeasts and lactic-acid bacteria, can be developed for improved industrial performance. For example, GM brewer's yeast strains have been created by introducing genes for starch-degrading enzymes. Such strains have improved fermentation characteristics and are used to generate

low-calorie beer^{14,15}. Most examples of GM food involve crop plants. These plants might be marketed whole, as in the case of GM tomatoes, or as processed food, as in GM tomato paste. In addition, a wide range of foods might include plant derivatives, such as flour or oil that are manufactured from commodity crops, including GM soya and GM maize. These various applications involve distinct safety issues and it is an important principle of regulatory practice that safety be evaluated on a case-by-case basis.

BOX 2 outlines the procedures that are used to introduce foreign DNA into a plant. The analysis of the introduced DNA is an important part of safety evaluation, and the method that is used to deliver DNA has been shown to influence its fate in the plant genome. Transgenes seem to integrate randomly and sometimes multiple tracts of DNA are inserted either at the same or at distinct sites. In addition, microparticle bombardment often results in rearrangement of DNA and recent results with GM soya indicate that small fragments of DNA might integrate at additional secondary sites within the genome¹⁶. Such events might be missed when using Southern hybridization or the polymerase chain reaction (PCR) to characterize the deliberately introduced DNA.

Molecular analysis should be extended to determine whether small tracts of transgenic DNA have unexpectedly integrated at secondary sites. This precaution has been taken for GM soya, in which it was established that the additional DNA was not expressed¹³. Microparticle bombardment has been the favoured approach for transforming plant species that are not amenable to *Agrobacterium* T-DNA delivery methods. Extending the host range of *Agrobacterium*¹⁷ should remove this limitation and reduce the risk that transgenic DNA will be rearranged.

The use of marker genes. Bacterial antibiotic resistance genes have been introduced into GM plants as selection markers for their primary transformation. The neomycin phosphotransferase 2 (*nptII*) gene, which confers resistance to the antibiotics kanamycin and neomycin, has been engineered for expression in plants, in which it is used frequently. Several regulatory bodies, such as the US Food and Drug Administration, have accepted arguments that the use of *nptII* does not compromise safety. This decision was based on the limited importance of both kanamycin and neomycin in the treatment of bacterial infections in humans, the already widespread distribution of the *nptII* gene in nature and the very low risk that the gene would transfer from plants to bacteria¹⁸.

Some GM plants carry antibiotic resistance genes other than *nptII*. In these cases, the antibiotic resistance genes have not been engineered as plant-selection markers and therefore retain their original bacterial promoter. Genes in this category include *bla* (β -lactamase ASE-1), *aad* (aminoglycoside adenyltransferase) and *nptIII*. All these genes confer resistance to antibiotics that have greater use in clinical medicine than kanamycin and neomycin. Because these genes are not directly selectable in plants, there is no good reason for their presence in GM material that is destined for use as food. As with *nptII*, it has been argued that antibiotic resistance is already widespread in bacteria, and so a rare gene transfer from a GM food source is unlikely to be of practical consequence. By contrast, even though the level of resistance to antibiotics is high, the situation might be so serious that no increase in antibiotic levels, however marginal, would be acceptable, especially when the gene retains a bacterial promoter^{19–21}.

Selectable markers can be removed from the genome of the modified plant (BOX 2). Transformation of trait genes and selection markers together, followed by segregation of the latter, has been effective in both transformation by *Agrobacterium*²² and by

Table 1 | Approvals of genetically modified foods in the UK and in Europe

Organism (company)	Genetic modification and use
Approvals made by ACNFP before Regulation (EC) 258/97	
<i>Aspergillus niger</i> <i>Kluyveromyces lactis</i> <i>Escherichia coli</i>	Engineered to express calf chymosin, which is used as a clotting agent in cheese manufacture. Widely used.
Baker's yeast <i>Saccharomyces cerevisiae</i>	Expresses maltose permease. Never commercialized.
Brewer's yeast <i>Saccharomyces cerevisiae</i>	Expresses the amylase gene to facilitate starch breakdown. Never commercialized.
Tomato paste (Zeneca)	Antisense expression of the polygalacturonidase gene to increase yield and reduce spoilage. Marketed in the United Kingdom but now withdrawn.
Processed derivatives of soya (Monsanto)	Engineered for tolerance to the glyphosate herbicide Roundup. Imported and used widely.
Processed derivatives of maize (Ciba Geigy)	Engineered to express <i>Bacillus thuringiensis</i> insecticidal protein.
Applications pending approval under Regulation (EC) 258/97	
Oil from oil seed rape (AgrEvo)	Tolerant to glufosinate ammonium herbicide.
<i>Bacillus subtilis</i> (Hoffman La Roche)	Engineered to produce Riboflavin.
Food-relevant approvals under Directive 90/220/EEC	
Chicory (Bejo-Zaden)	Male-sterile and tolerant to glufosinate ammonium herbicide. Used for breeding activities.
Applications pending approval under Directive 90/220/EEC	
Potato (Amylogene)	Altered starch composition.

Across Europe, the approval of genetically modified (GM) food is controlled by EC Regulation 258/97 on 'Novel Foods and Novel Food Ingredients'. At present, all applications under this Regulation are pending. Before this Regulation, the Advisory Committee on Novel Foods and Processes (ACNFP) approved the commercialization of several GM foods within the United Kingdom. Deliberate releases into the environment, including the agricultural use of GM crops, are controlled at a European level by Directive 90/220/EEC. The table gives examples of these approvals and pending applications. A more complete data set is available in the EC release 'Facts on GMOs in the EU'.

microparticle bombardment¹⁹. The *CRE/LOX* system²³ has been used to facilitate the physical removal of selection markers after the construction of GM plants.

The exploitation of antibiotic selection markers, especially *np_{III}*, is widespread in plant transformation, and GM plant material that carries antibiotic resistance genes continues to be put forward for consideration by regulatory authorities. However, alternative approaches that avoid the use of antibiotic resistance are being developed, including the Novartis 'Positech' marker system that relies on a gene for phosphomannose isomerase and uses selection for growth on mannose²⁴. However, it should be ensured that these alternative selection methods do not raise different concerns.

Fate of consumed DNA. There are concerns that transgenic DNA might be transferred across the gut wall of the host, and lead to genetic alteration of that host. This argument has its supporters, despite the fact that we eat large amounts of DNA in our everyday diet, and do not, for example, sprout tomatoes from any bodily orifice! There have also been (scientifically unfounded) concerns that the strong plant virus promoter used to express

transgenic DNA might be active in mammalian cells. One of the best-established barriers to such transfer is the sensitivity of DNA to inactivation and degradation. In the case of food, deoxyribonuclease I that is produced by the salivary glands, pancreas and small intestine is a potent degradative enzyme; furthermore, the low pH of the stomach should eliminate any biological activity by removing adenine and guanine residues. Although DNA might be degraded after consumption, recent work indicates that small amounts might remain intact, and that this level might be enough to generate a low frequency of bacterial transformants²⁵. DNA might not be degraded sufficiently fast in the mouth to rule out transfer of DNA — including any transgenes — to oral bacteria. However, transformants would be found only in the presence of a mechanism for DNA maintenance in the recipient bacteria. Recently, Chambers *et al.*²⁶ investigated the fate of the ampicillin resistance gene (carried on the pUC18 plasmid) in chickens after feeding them GM *E. coli* and GM maize both of which contained the ampicillin resistance gene. They found that the maize gene was present in the mouth but not further down the gastrointestinal tract,

whereas the bacterial gene was protected by its host and remained detectable throughout the gastrointestinal tract.

In a series of experiments^{27–29}, M13mp18 duplex circular DNA and bacterial plasmid DNA were fed to mice. DNA fragments were shown to survive in the gastrointestinal tract, enter the bloodstream, with small amounts even entering cells and establishing covalent linkage to cellular DNA. The significance of these results has been questioned³⁰, in part because the bacterial DNA used for these experiments was unmethylated and contained sequences likely to cause upregulation of inflammatory cell activity, thus contributing to the detection of the introduced DNA by the immune response.

It is relevant to consider the effect that processing and cooking might have on DNA in GM food material as well as conditions that might influence the uptake by and transfer of DNA across the gut wall. It is counterintuitive that transgene DNA should behave differently to any other DNA, and data on DNA survival are of little significance in assessing the safety of GM technology *per se*. Clearly the trait encoded by transgenic DNA should be of greatest concern when considering its survival and its potential transfer.

Gene transfer. Another area of concern is the acquisition of transgenic DNA by microorganisms that inhabit the gastrointestinal tract or, in the case of the environment, by the soil or the plant RHIZOSPHERE. The most likely route by which transgenic DNA could be transferred to bacteria is by DNA release and natural transformation. Lorenz and Wackernagel³¹ have extensively reviewed the status of bacterial gene transfer by natural genetic transformation in the environment. The limited number of studies that have investigated DNA transfer from GM plant material to microorganisms³² tend to confirm the view that such an event would be extremely rare, but not impossible.

Schluter *et al.*³³ used the plant pathogenic species *Erwinia chrysanthemi* as a recipient for the DNA that had been introduced into plants. In this model system, a transgenic potato carrying a chromosomally integrated transgene was used, and the plant pathogenic property of *Erwinia* provided an intimate association between the plant material and the potential bacterial recipient. No evidence for plant-to-bacterium transfer was found in this study. DeVries & Wackernagel³⁴ used naturally competent *Acinetobacter calcoaceticus* and a marker rescue strategy with various transgenic plant species. They found that the artificial provision of recipient homology to transgene DNA facilitated efficient gene

Box 2 | Overview of techniques used in the construction of genetically modified (GM) plants

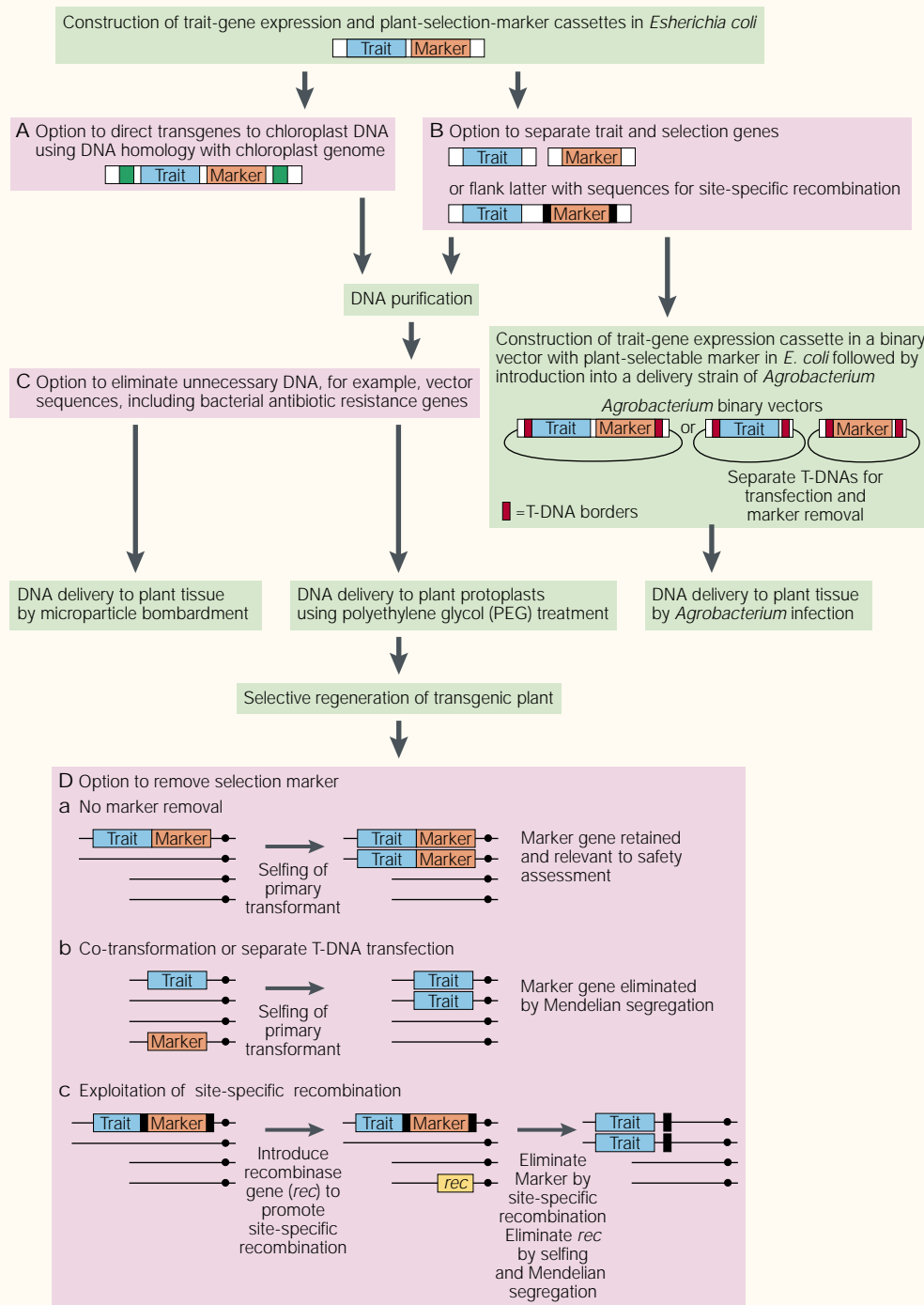
The following options influence safety and containment:

A The use of a vector designed to deliver transgenic DNA into the plant chloroplast genome by homologous recombination provides controlled integration at a known site. In addition, the lack of chloroplasts in pollen contributes to the environmental containment of transgenes.

B The introduction of trait and plant selection genes on separate DNA fragments facilitates their unlinked integration in the plant genome. Alternatively, the plant selection gene can be flanked by sequences that are recognized by site-specific recombinases (for example, the Cre recombinase and the *lox* recognition site). In both cases, subsequent elimination of the selection gene is possible using conventional plant crosses (see D).

C Although the elimination of unnecessary DNA that was used during propagation in bacteria is straightforward, such a procedure has not always been undertaken. This has led to complications arising from the presence in the plant of antibiotic resistance genes and from more complex rearrangement of trait DNA.

D The marker elimination process described in point B is realized by conventional crosses that facilitate the segregation of trait and selection genes. For site-specific recombination, the elimination of the marker gene is achieved by introducing a recombinase gene from a separate GM plant. The recombinase gene can be subsequently removed through a conventional cross.



transfer by natural transformation but that, in the absence of this homology, transformation efficiency was below the limits of detection. Similar results were obtained using DNA from GM sugar beet³⁵. Several unpublished studies might provide direct evidence for the transfer of DNA from transgenic plant material to native bacteria under natural environmental conditions. One example is DNA acquisition from GM pollen by a yeast strain

that inhabits the intestinal tract of bees³⁶. However, the significance of this and other preliminary findings will need to be established by peer review.

The study of the transfer of genes from genetically modified plants to other plant species has aroused intense interest and has contributed to recent attacks on GM crop trials in the United Kingdom. There seems to be no evidence that gene transfer leads to WEEDI-

NESS, and pollen transfer, which can occur only between sexually compatible plants, seems no more extensive than that occurring between untransformed plants. Thus, there is no evidence that the presence of a transgene affects pollen transfer. As organic farming groups have declared that no 'contamination' of their crops with genetic material from GM plants is acceptable, it is difficult to see how scientific evidence can be used to resolve the

issue. The future use of TERMINATOR TECHNOLOGY or the exploitation of plastid transformation (BOX 2) might provide assured genetic containment, but our view is that the organic groups are concerned mainly with identity preservation, rather than safety.

The occurrence of a gene transfer event, whether to microorganisms or related plant species is, in itself, unlikely to be of any great significance unless it confers a selective advantage on the recipient. Conversely, the existence of selective advantage could make even a very rare genetic event important. Safety evaluation should emphasize the nature of traits that are encoded by the introduced DNA and any consequences that might arise from its unlikely transfer, rather than from the transfer process itself.

The effect of the introduced trait. The introduced transgene might influence the phenotype of the plant in two possible ways: by direct expression of the transgene or, indirectly, by affecting the expression of other genes. The consequences of the first are relatively straightforward to test using an analysis of the transgenic protein for function, toxicity, allergenicity and antinutritional effect. One caveat is that differences in post-translational processing in the plant, compared with the organism from which the transgene was derived, might affect the properties of the protein. The second possibility — that the

“Many consumers eat GM foods. No significant adverse effects have yet been detected on human health.”

transgene might affect the expression of other genes in the plant — is much more difficult to anticipate, detect and evaluate, and is discussed below.

Testing for potential toxicity uses highly developed procedures and the accumulated experience of many years. By contrast, testing for potential allergenicity is complicated by the heterogeneity of the population at risk; for it is well known how serious, but rare, some allergies are. There are three ways in which the potential allergenicity of a new protein can be tested: first, allergens tend to be heat-resistant; second, they resist digestion by enzymes of the gastrointestinal tract; and last, some allergens can be recognized by their amino-acid sequence — a process that is facilitated by the growing number of protein databases.

Over the past ten years, no introduced GM crop or food has raised problems of this kind (see REF. 37 for a recent review). However, the safety evaluation of allergenic potential is challenging and it is appropriate that a network of over 30 scientists, including clinicians, food scientists and plant biologists has been set up recently “to study the problems of food allergy”³⁸. The recent, highly publicized withdrawal of taco shells from the US market arose because, although the regulators had cleared the GM maize for animal feed, it had not been cleared for human use. That decision was based on the possibility that the product might be allergenic, based solely on the resistance of the transgene product in digestion tests (one established property of allergens)³⁹.

Unintended effects. The substantial equivalence concept aims to reveal unintended consequences of genetic modification by comparison of a GM derivative with its conventional counterpart. This approach has been adequate to date, but there are concerns that this practice might be insufficiently robust to deal with cases that involve the introduction of multiple traits or the manipulation of a more complex metabolic trait. As gene technology progresses from modifications aimed at relatively simple agronomic traits to address more complex quality attributes, the challenges to evaluate unintended effects will increase. Attempts are being made to improve the safety evaluation of possible

unintended effects of transgene introduction and to establish consistent guidelines as to the appropriate targets for comparison (BOX 1).

It is curious that the public accepts the products of conventional plant breeding without this detailed evaluation of unintended effects. This ignores the fact that conventional breeding can involve treatments, such as mutagenesis and induced polyploidy through colchicines, which are more likely to cause unintended changes in gene expression⁴⁰.

Post-market monitoring
Public concerns, largely due to the efforts of green pressure groups, have raised calls for post-market monitoring of GM foods. The initial debate has shown that this is not easy. There are two problems: the first is the difficulty of collecting data about which members of the population have been eating GM foods — a proposal in the United Kingdom to use supermarket ‘loyalty’ cards was rejected on grounds of the invasion of privacy. The second problem is that any GM foods present in the diet of any population will be derived from such a range of crops and processes, and present in such a large range of foods that it will be extremely difficult, if not impossible, to correlate consumption of a particular GM food with any recognizable syndrome. It is already clear from the experience of the United States, in which many people have been eating products that contain GM soya and GM maize for several years, that any effects will be small, if present at all. How could such effects be detected? The idea of monitoring a large population that eat GM products with an equally large and matched population of those that do not eat GM products is daunting and might be incommensurate with the risk.

It is also appropriate to consider post-market monitoring of environmental effect. This would address concerns about outcrossing and the evolution of resistant pests as well as substantiating claims of benefits from the use of GM technology.

Conclusions

GM food is a collective term that includes a range of distinct applications of modern biotechnology, ranging from cell factories for the production of ingredients identical to their natural counterparts through to the provision of GM fruits to be eaten fresh and unprocessed.

In this article, we have highlighted areas where more science data and technology development is desirable. Issues of importance include finding alternatives to antibiotic resistance marker genes and tackling the

Glossary

CALF CHYMOSIN

Active ingredient of rennet, used to clot milk during cheese manufacture. It is a proteolytic enzyme that breaks the milk protein k-casein, thereby effecting a change in texture.

CRE/LOX

A site-specific recombination system derived from *Escherichia coli* bacteriophage P1. Two short DNA sequences (*lox* sites) are engineered to flank the target DNA. Activation of the Cre-recombinase enzyme catalyses recombination between the *lox* sites, leading to excision of the intervening sequence.

RHIZOSPHERE

The region in the soil surrounding the root system of a plant, affected by the excretions from the roots and characterized by considerable microbiological activity.

SUPERWEEDS

Plants with a genetic predisposition to aggressive weediness. This can be induced unintentionally by genetic modification.

TERMINATOR TECHNOLOGY

Genetic modification intended to prevent a GM plant cultivar from setting seed.

WEEDINESS

Tendency of a plant to grow where it is not wanted by humans.

problem of transgene rearrangement when plants are transformed using microparticle bombardment. The evaluation of allergenic potential of GM foods remains challenging and the analysis of unintended effects might become more difficult as the complexity of the introduced trait increases. Molecular-profiling methods show promise but their practical value remains to be established. The public desire for post-market monitoring is difficult to address with worthwhile scientific investigations and it might be that the experience of the US consumer is a more effective source of data.

Finally, the perception of risk is an aspect that is especially important and this social and psychological dimension seems to have more effect than the scientifically defined risks that are addressed in the detailed safety evaluation to which GM food is subjected. It is relevant to emphasize that this safety evaluation is far more thorough than that which is applied to new food materials produced by conventional plant breeding that have been safely introduced into the food chain over decades.

Michael Gasson is at the Food Science Division, Institute of Food Research, Norwich Research Park, Colney, Norwich NR4 7UA, UK. Derek Burke is at 13 Pretoria Road, Cambridge CB4 1HD, UK. Correspondence to D.B. e-mail: dcb27@hermes.cam.ac.uk

 Links

FURTHER INFORMATION **Substantial equivalence** | **Royal Society critique of Pusztai's experiments** | **Facts on GMOs in the European Union** | **OECD** | **WHO** | **FAO**

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SCIENCE AND SOCIETY

Human genome diversity: What about the other human genome project?

Henry T. Greely

Although the Human Genome Project has been successful, the Human Genome Diversity Project, proposed in 1991, has so far failed to thrive. One of the main values in studying the human genome, however, will come from examining its variations and their effects. To do that in a systematic way, an active Human Genome Diversity Project, or something very similar, will ultimately prove vital. Such an effort will confront difficult ethical and political issues; this article reviews those issues and tries to show how they might be overcome.

In the summer of 1991, when the Human Genome Project (HGP) had only just been launched, scientists interested in human population genetics issued a call in the journal *Genomics* for the formation of a parallel project, to explore not just a single 'consensus' human genome but the diversity of the more than 11 billion human genomes then existing in the world¹. This Human Genome Diversity Project (HGDP) would require only a fraction of the money and time needed for the HGP; the organizers estimated that it could be accomplished in 5 years for