



The great food gamble

**An assessment of
genetically modified
food safety**

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May 2001

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Executive summary

People's concerns about GM foods are deep-seated and long-standing. Food crises such as the BSE disaster have undermined the credibility of the scientific and regulatory establishment. Biotech companies and the regulatory authorities consistently claim that GM crops are safe to eat because they are subjected to a thorough and rigorous testing. This document outlines the system to which GM crops are subject and details the many gaps in understanding, technical expertise and procedure which exist. Indeed, so poor is the faith of regulators in their own systems that monitoring systems are being proposed in order to pick up health effects after GM crops have been approved for use in food. It is the conclusion of this report that the safety assessment process, as it stands, is not adequate to pick out every GM crop harmful to human or animal health.

The challenge of GM foods

There is a distinct difference between GM crops and those produced by traditional selection breeding. Selection breeding moves genes around within a species by crossing varieties together, genetic modification introduces genes from other species, even very distant ones. Whatever technique is used to insert novel genes, the genetic constructs are inserted at random into the host's genome. The imprecise and blunt genetic regulation mechanisms associated with novel genes contrast sharply with the tight and precise control of native genes. Finally, because of the expense of developing novel genetic constructs, the same novel genes are often inserted into many different crops, with the result that the same novel proteins are present in a wide range of foods.

Due to the uncertainties inherent in genetic modification, the effects on GM organisms are often undesired and unexpected. Documented effects include disruptions to the metabolism - alterations in the composition of GM crops have, in some cases, been observed for ones already on the market. Functional GM foods are being developed, such as vitamin A-producing rice, in which complicated genetic modifications aim to change the metabolism of the plant. This greatly increases the chances that unexpected changes in metabolism and composition will occur.

Substantial equivalence

The Royal Society of Canada recently reported that the use of substantial equivalence is "scientifically unjustifiable". Substantial equivalence is the concept which underpins the safety assessment of GM crops around the world. The basic premise is that if a GM food is shown by composition analysis to be the same as a non-GM food then it should be considered to be as safe as the non-GM food. However, GM foods cannot be exactly the same as non-GM foods, by the very fact of the novel proteins they contain, and so it was determined that they would be considered as safe as normal foods if they were substantially equivalent to them. However, there has never been any meaningful definition of 'substantially', and this has led to

constant differences in interpretation. Interpretations of substantial equivalence vary around the world, meaning that GM crops may be deemed substantially equivalent in the US but not in the EU. These difficulties are likely to increase as GM crops become more complex.

Establishing the safety of GM foods

There is a large difference between our ability to create GM crops and foods, and our ability to test whether they are safe to eat. At present, examination of GM foods concentrates on simple chemical composition analyses. But this approach is criticised as being far too crude. It cannot detect unexpected or novel toxins as it focuses only on the known constituents of the food, and in many cases even the analysis of the levels of the known anti-nutrients is not done adequately, or at all. Understanding of the impact of food constituents is constantly changing, further hindering interpretation of observed results. New techniques for analysing GM foods, such as looking at genetic activity, total protein production and metabolic activity have been proposed but such techniques have not been applied to GM foods already on the market or in the pipeline.

Similarly, there are no established predictive tests to establish whether or not a novel protein may cause allergies. At present, companies rely heavily on theoretical assessments while the regulatory authorities have suggested monitoring for allergies after the food is released onto the market.

Animal tests have been used to support safety claims for GM foods and crops. However, the majority of these tests have been undertaken by biotech companies, and very few have been published or peer reviewed. In one case, the company has consistently refused to make public the detailed results of its studies. In another case, the same unpublished study was used to support GM crops produced by different companies. In a further case, when the company did make its research available for peer review, the study was severely criticised and the reviewers pronounced that in their opinion it was unfit for publication. Only a tiny number of safety assessments of GM foods have been published, and most remain unavailable to the public.

The US's guinea pigs

The US has the widest range of GM crops on the market and more than half of the US maize and soybean crops in 2000 were GM. Until May 2000, there was no statutory oversight of GM crops in the US, only a voluntary consultation procedure. More than 45 GM crops, containing at least 28 novel proteins, are listed by the Food and Drug Administration (FDA) as on the market. A number of applications for GM crops already marketed in the US have been severely criticised or rejected in the EU.

As there is no labelling of GM foods in the US, monitoring of health effects is impossible. Health effects might not become apparent immediately anyway, even if the authorities were attempting to monitor them. The case of allergic reactions reported after the consumption of products containing the GM maize Starlink was unusual simply because consumers were made aware that they were eating it. This is not usually the case, and so consumers would not be

able to make any connection between health effects and GM food consumption - this means self reporting is almost useless.

Conclusions

Enormous amounts of time and effort have been spent by governments and the biotech industry in presenting GM crops and foods as being well-regulated and as safe as non-GM foods. Yet there are specific hazards which arise from GM foods distinct from those arising from non-GM foods. Firstly, there is the possibility, as a result of genetic modification, of significant alterations to the metabolism of GM food plants. Secondly, there is the fact that most novel proteins inserted into GM crops are entirely novel in the food chain, and that these are being placed into a wide range of food crops. The conclusion of this report is that the current system is unable to address these specific hazards satisfactorily.

Friends of the Earth believes the safety assessment of GM crops must be subjected to full review in light of the following:

- GM crops are not the same as those produced by traditional selection breeding, because of the random nature of genetic modification and the uncertainty of its consequences
- the ability to detect differences in native genetic activity caused as a result of genetic modification, and understanding of their consequences, lags far behind the rate of development of GM crops
- difficulties in assessing the impacts of genetic modification will intensify as modifications become more complex.

Furthermore, Friends of the Earth believes the following procedures and practices are unacceptable:

- the presence of antibiotic resistance marker genes in a wide range of GM crops
- the use of substantial equivalence as a tool for assessing the safety of GM crops and foods
- the reliance on simple chemical analysis for examining the composition of GM crops and foods
- the reliance on theoretical analyses for establishing the allergenicity of novel proteins
- the use of inappropriate animal testing in support for the safety of GM crops and foods
- the withholding from public scrutiny of detailed safety assessments by biotech companies.

Friends of the Earth believes this system of oversight cannot guarantee the safety of GM products on the market. Gaps exist in regulatory procedures and their theoretical underpinnings, the information provided in support of GM crops, and the ability to test the

safety of GM foods. It is frequently argued that there is no evidence that GM foods are any more dangerous than non-GM ones, and yet there is little credible scientific evidence to support this. It is possible that many GM foods are as safe as their conventional counterparts, but the system is not in place to make this judgement, nor is it adequate to detect any GM food that might be a long-term danger to consumers and farm animals.

1. Introduction

Food produced from genetically modified (GM) crops has become one of the biggest disputes in the already controversial area of food and agricultural production. Considerable time and money has been spent by the biotechnology industry, scientific community and Government to convince a doubting public that there is nothing to worry about, but while GM crops have been widely adopted by producers in the US, consumers in the European Union and Japan have reacted strongly against them. This consumer resistance is often portrayed by GM proponents as having been whipped up by public interest groups. This is not true. Concern over the safety of GM crops and food has come largely from consumers themselves, as researchers from Lancaster University found in 1996 before to any great public debate about the GM issue in the UK:

“People’s immediate responses to genetically modified foods, outside the context of particular products, tended to reflect unease at inadequately restrained meddling with nature, and questioning of intentions. Analogies were drawn with other experiences of food and the risks of genetically modified foods were expected to be analogous in character to those brought about by chemicals and industrial systems of food production - additives and BSE being the most commonly used examples”.¹

The level of concern and resistance to GM foods from consumers appears to have shocked the biotechnology industry and many scientists, yet it is clear from this early public opinion research that concerns about the safety of GM foods are deep seated. They range from the moral and ethical implications of genetic modification, to concerns about the environmental impact of the spread of modified genes, from changes in agricultural practice to the impact on poor farmers in developing countries. They include fears about the safety of the foods derived from GM crops. The scientific and political establishments have been consistently slow to accept the public’s concerns and attempts to address them have been inadequate.

Consequently, claims that regulatory procedures ensure the safety of GM crops have remained unconvincing. At least in the UK, the credibility of Government and industry has been severely weakened by the mishandling of BSE in UK cattle and the subsequent development of new variant Creutzfeldt Jacob Disease in humans. As was found in the Lancaster study: “Government and industry were not thought to share consumers’ interests in food safety, but rather to engage in promoting their shared self-interest through mutual support.”

The risks from GM foods in terms of human health remain uncertain because so little is understood about this technology and its impacts. Lord Phillip’s report into the UK’s BSE crisis highlights the difficulties encountered when dealing with a risk that is uncertain in outcome and which could take many years to become apparent. It notes that:

“When responding to public or media demand for advice, the Government must resist the temptation of attempting to appear to have all the answers in a situation of uncertainty. We believe that food scares and vaccine scares thrive on a belief that the Government is withholding information. If doubts are openly expressed and publicly explored, the public is capable of responding rationally and is more likely to accept reassurance and advice if and when it comes.”²

Despite this clear warning, public authorities and industry representatives around the world continue to avoid real debate. While Government, industry and the scientific establishment have made repeated public statements about the safety of GM crops and food, as well as the security of assessment procedures, the safety of GM foods and the effectiveness of regulatory procedures continues to be questioned, both from without and from within. At a conference organised by the Organisation for Economic Cooperation and Development (OECD) in 2000, it was accepted that:

“There remains uncertainty about the potential long-term effects of GM food on human health ... Current methods for testing toxicity and allergenicity ... leave some uncertainties and need to be improved.”³

The development of new GM crops and foods is continuing apace. Attention is increasingly focused on the development of functional foods, such as those containing increased vitamin content, in an attempt to win over consumers. Yet, while companies clearly hope that the new types of GM crops will improve their image with the public, such GM crops pose an even greater challenge in terms of assessing their safety as foods. It is essential that there is a real, open and frank debate about the safety of GM crops, and whether we have the knowledge or technical ability to judge the consequences of eating foods derived from them. This document aims to provide a trigger for just such a debate.

2. The challenge of GM crops

“The breeder’s dream is, of course, of an agency or agencies which would enable him to produce at will a particular kind of mutation uncontaminated by others which would merely be a nuisance to him.”

Mather, 1960⁴

For thousands of years, farmers and plant breeders have been changing crop plants to improve characteristics such as size, appearance and taste. This was done by taking advantage of the natural variation found in the different populations of crop plant species. Plants which grew well, had a higher yield or tasted better, were selected and bred from. This process, known as selection breeding, is still the most widely used technique for developing new plant varieties within a particular crop species. Between different species there are natural barriers which prevent cross breeding, so selection breeding is only able to make use of the genes and characteristics that are naturally present in the different populations of one crop species.

Over the centuries, these valued characteristics have been concentrated into particular varieties by the breeding process. By the middle of the twentieth century, plant breeders were seeking ways to extend the range of characteristics available to them. For example, attempts have been made to induce mutations in the genetic make-up of plants, by irradiation or the use of chemicals, in the hope that this would create new and useful characteristics in the plants. But the use of such techniques has not been widely adopted, mainly because most mutations cause worse rather than better characteristics in the plants, and by 1991 ‘mutation breeding’ had only produced 1,500 registered varieties of plants and micro-organisms around the world.⁵

In their most recent attempt to improve our food crops, scientists and plant breeders embarked on the process of genetic modification, in which genes are moved between unrelated organisms, with the aim of introducing specific new traits of commercial value. The differences between this and selection breeding are outlined below.

Getting novel genes into plants

Within every cell of every organism is the biological code for its construction. This code is held within the structure of an extremely long chain molecule, deoxyribonucleic acid (DNA), which contains all the information necessary for the growth, maintenance and development of the organism. This code can be broken down into small segments controlling specific functions, and these are referred to as genes. Very simple organisms, such as bacteria, may have a few thousand genes, while more complicated organisms have many more - it has been estimated that maize has around 50,000 genes. The long DNA molecule is tightly packed into a structure called a chromosome, and higher organisms have more than one of these tightly packed bundles of DNA, each one containing masses of genetic information. The collective term for all of the genetic information in an organism is the genome.

Transferring DNA and genes from one organism to another is a difficult procedure. In early attempts it was realised that one of the main problems would be getting past the natural

defences of plant cells. Different techniques were developed in order to do this, such as shooting tiny metal balls coated with DNA into cells (particle bombardment) or mixing DNA with cells from which the cell walls had been removed (protoplast transformation). But the most commonly used technique involves a bacterium called *Agrobacterium tumefaciens* (*A. tumefaciens*). This bacterium already possesses the ability to get past plant cell defences, as it causes cancerous growths in plants, called crown galls. It does this by transferring its own genes into plant cells through wounds and the genes incorporated into the chromosomes of the plant cells, causing them to become cancerous.

Genetic modification effectively hi-jacks *A. tumefaciens*: in order to get novel genes into plants, the cancer causing genes are removed from *A. tumefaciens*, and novel genes put in their place. The bacterium then transfers these into the plant cell. After this transfer has occurred, the bacteria are killed using an antibiotic. However, recent research for the UK Government found that *A. tumefaciens* bacteria are not killed by antibiotics that have been applied after the genetic modification of plant cells has taken place.⁶ Regular checking for the presence of the modified agrobacteria does not take place during the development of GM plants - it is assumed they have been killed. Yet it was found that the bacteria could survive for up to 13 months inside the transformed plants, as well as in plants derived from them, and after six months 12.5 per cent of these bacteria still contained the novel genes. They were found to be still capable of transforming cells in the plants they were infecting.

A haphazard process

Whatever means is used, the insertion of novel genes into the plant cell is a fairly haphazard process. There is no way to control or direct what happens - new genes end up being inserted randomly into the genetic makeup of the host organism. In fact, the operation to insert new genes frequently fails - inserted genes fail to work, behave in ways that aren't expected, or the functioning of native genes may be affected.⁷ There is no means of controlling where the genes will end up within the chromosome, and in many cases more than one copy of the gene may be incorporated, or extra DNA from the bacterial plasmid may get incorporated as well as the novel genes. In many organisms, including wheat, maize and rice, DNA is divided into active regions of working genes and the so-called junk DNA that does not show any activity. In a recent experiment using rice, it was found that novel genes only integrated into this active, gene rich region of the genome.⁸ In other words, the novel genes always ended up in the area where there were already genes working. It is now known that genes do not work in isolation, in fact they often work in groups, and their neighbouring genes can affect how they work. Because of this, the insertion of a novel gene into an active genetic region will always have the potential to cause disruption to the genetic functioning of the organism.

Many crops - the same genes

It is only rarely that genes are sourced from the crop species being modified, and often they come from extremely distant organisms, such as bacteria. Sourcing and developing novel genes can be a time-consuming and expensive process so, once isolated, the same genetic sequences are used time and again. This means that the novel proteins produced by these genes end up in a wide range of GM crops.

Some common Novel genetic sequences in GM crops and their sources

Genetic sequence	Novel protein produced	Source	GM crops it is used in
pat	Phosphinothricin Acetyl Transferase - an enzyme which breaks down the herbicide glufosinate ammonium, which is made by Aventis	Bacterium: Streptomyces viridochromogenes	Aventis 'T25' & 'T14' Liberty Link GM maize varieties Aventis GM oilseed rape varieties derived from Falcon 40/90 Aventis Liberator Hoe6 GM oilseed rape varieties Aventis 'T45' GM Liberty Link oilseed rape Novartis/Northrup King GM 'Bt 11' maize varieties Aventis GM oilseed rape Topas 19/2 Aventis Liberty Link soybean Aventis Liberty Link sugar beet
bar	Phosphinothricin Acetyl Transferase - an enzyme which breaks down the herbicide glufosinate ammonium, which is made by Aventis	Bacterium: Streptomyces hygroscopicus	Plant Genetic Systems GM oilseed rape MS1xRF1 Bejo Zaden's GM chicory Novartis' GM maize 'Bt 176' Aventis GM oilseed rape MS8xRF3 Dekalb GM maize DTB418
cp4 EPSPS	Bacterial version of the enzyme EPSPS. Unlike the plant's own EPSPS enzyme, this is resistant to the herbicide glyphosate, allowing crops tolerance to the herbicide	synthetic version of a gene originally from bacterium: Agro-bacterium subsp CP4,	Pioneer Hi Bred GM maize MON809 Monsanto Roundup Ready soya 40-3-2 Monsanto Roundup Ready sugar beet A5/15 Monsanto Roundup Ready Cotton line 1445 Monsanto Roundup Ready oilseed rape Monsanto 'Insect Protected' maize
CryIA(b)	'Bt' toxin or delta endotoxin. This is toxic to various insect species, including the pest European corn borer	Bacterium: Bacillus thuringiensis subsp. Kurstaki strain HD1	Monsanto GM maize MON810 Novartis GM maize 'Bt 176' Monsanto maize MON 809

Controlling novel genes

Under natural conditions, the characteristics of a crop plant, such as the size of fruit, are controlled by groups of functionally related genes, which provide a co-ordinated control of the characteristic. These genes are bound up with associated 'regulatory' sequences of DNA, which ensure that the genes work in the right part of the organism and at the right stage of its life cycle. These have evolved along with the genes they are attached to and so they are specific to the plant species, or even to the genes, providing a very tight control over the functioning of the genes in the organism. During traditional selection breeding, these groups of genes are moved around within the plant population and concentrated into a particular plant line by crossing different varieties together.

In contrast, genetic modification tends to use single genes from species other than the crop plant to get the desired characteristic. These novel genes also need regulatory sequences attached to them so that they will work in the plant. But very few of the regulatory sequences in plants have been fully described, and without the right regulatory sequence the introduced genes will not function as desired. To get around this problem, genetic engineers have been forced to use short cuts - such as using regulatory sequences from viruses. Viruses attack organisms by taking over the genetic machinery of an infected cell, and reprogramming it to make more viruses. To achieve this, the virus genes must have regulatory sections that the genetic machinery of the infected cells will be able to understand. This has proved convenient for genetic engineers, and viral regulatory sequences are often attached to the novel genes inserted into GM crop plants. The viral regulatory sequence allows the novel gene to work in the GM plant even though it hasn't got the 'right' regulatory sequence from the plant itself.

Unnatural expression

One of these viral regulatory sequences is known as the 35S promoter sequence, taken from the plant pathogen Cauliflower Mosaic Virus (CaMV). It has proved to be very successful at allowing inserted genes to function, but because it comes from a virus rather than the crop plants, it is not nearly as precise as the native regulatory sequences. In fact, the CaMV promoter is extremely powerful and, if inserted successfully, causes the inserted novel genes to be 'on' in every cell of the plant, as well as allowing expression of the novel gene at very high levels. It is effective, but it is a blunt instrument in terms of genetic regulation. In contrast to the precise and controlled action of the native genes, inserted genes linked to the CaMV promoter may be on at full blast in every cell of the organism from the moment of fertilisation through to death - meaning that the novel protein is produced at high levels in the plant through out its life. This is completely at odds with natural genetic functioning and the consequences are largely unknown. More precise regulatory sequences are being developed, but CaMV is still the most commonly used promoter in GM crops, in part because it is in the public domain and therefore there is no need to pay royalties for its use. In fact, the popularity of this blunt instrument promoter is illustrated by the fact that the vast majority of GM crops on the market, or close to marketing, contain this construct.

Getting novel genes to work

“Mankind is in the first millimeters of a 1000 km journey of understanding.”

Adrian Dubock, Astra Zeneca⁹

Because novel genes are inserted at random, they can have unpredictable and unexpected impacts upon the genetic function of the host organism. There is increasing evidence that genes interact and work with each other rather than being single isolated units and the inserted novel genes can impact on the functioning of nearby native genes. Alternatively, native genes can affect the functioning of the inserted genes, and in some cases cellular defence mechanisms may cause inserted genes to be switched off - referred to as silencing. At present, the function of most native genes in crop plants is unknown - gene mapping can establish what genes are present, but even then the function of mapped genes is often unclear and scientific knowledge is a long way from explaining which genes are working together and how they interact.

Unexpected effects

There is no guarantee that inserted novel genes will behave as expected in every case. Concern has been widely expressed that their insertion could disrupt the genetic functioning of GM crop plants in such a way that unexpected toxins could be produced, or the levels of nutrients and naturally occurring toxins altered. Theoretically, the possibilities include the disruption or alteration of the expression of genes native to the plant - increasing or decreasing levels of naturally occurring nutrients or toxins. The novel gene could also cause a naturally occurring but silenced gene to be switched on, perhaps producing an unexpected toxin or new biochemical pathway within the plant. Or, production of a novel protein as the result of gene insertion could divert resources away from the normal metabolic pathways of the plant.¹⁰ This is not only a theoretical concern - there are many examples where genetic engineering has altered the composition of GM plants in entirely unexpected ways.

- Researchers at the University of Oxford who were working on cell metabolism, genetically modified potatoes to have low levels of the NAD-malic enzyme. They thought this would help them to understand cell respiration, but instead they unexpectedly created high starch potatoes. The head of the department was quoted as saying: “We were as surprised as anyone. Nothing in our understanding of the metabolic pathways of plants would have suggested that our enzyme would have such a profound influence on starch production.”¹¹
- Attempts to introduce beta carotene (the precursor to vitamin A) into oilseed rape led to reduced levels of tocopherols (including vitamin E) as well as alterations to the fatty acid composition of the seeds.¹²
- When researchers in Germany tried to boost the starch content of potatoes using genes from yeast and bacteria, the starch content actually fell, and several other compounds were produced due to the disturbance of the metabolism of the potato.¹³

These are examples from experimental GM crops, but they illustrate that the insertion of novel genes can have wider effects than those desired by scientists. There is also some evidence of

changes in composition of GM foods that have been approved for sale in the US, Europe and elsewhere. Information is scarce and little is available to the public, but there appear to have already been cases where the nutritional composition of a GM crop is different to the conventional crop from which it was developed.

Cases in which compositional changes in GM foods have been identified

Company	GM crop	Reported changes in composition	Approval
Monsanto	Glyphosate-resistant soybean	Altered levels of phytoestrogens ¹⁴	EU - 1996 US - 1994
Zeneca	Tomato with altered ripening	Changes in level of lycopene ¹⁵	EU- application for approval submitted US - 1994
Novartis (Ciba Geigy)	Insect-resistant (Bt 176) maize	“Sporadic statistically significant differences between the genetically modified maize and control maize ” (details withheld by company) ¹⁶	EU - 1996 US - 1995
Aventis	Glufosinate-tolerant T25 maize	Differences in amino acid composition and significant differences in fatty acid composition ¹⁷	EU - 1998 US - 1995
Pioneer Hi-Bred	Insect-resistant (Bt) maize	Significant differences in fat levels from non GM control. Statistically significant differences in the amino acids cystine and threonine and fatty acid linolenic acid from control. Stat. control changes in composition ¹⁸	EU - 1998 US - ?

Problems ahead

There has been much discussion recently about the proposed benefits of so-called functional GM foods, which the biotech industry hopes will convince consumers that there are real benefits from GM crops. Proposals include: oilseed rape producing high lauric acid oil; high vitamin A ‘golden’ rice; high oleic acid content soybean; potatoes with altered levels of starch; sugar beet with high levels of the “low calorie sugar” fructans; and rice with increased iron.¹⁹ Yet while there may appear to be consumer benefits from such foods, their production requires modifications to the basic metabolism of the plant. This means that the potential for unexpected alterations to the plant’s composition is far greater.

For example, white rice does not contain beta carotene, which is converted to vitamin A when eaten, because no metabolic pathway exists in rice to produce beta carotene in the endosperm (white part) of the grain. However, a team from the Swiss Federal Institute of Technology has genetically modified rice to do just this. The production of beta carotene in rice was not simple, requiring four new metabolic reactions in the plant, each one controlled by an enzyme that rice does not naturally produce. A complicated set of genes from daffodils and bacteria was inserted to create the GM rice.²⁰ Inevitably, such a complex alteration to the metabolism of the plant significantly increases the likelihood that the metabolism will be altered in ways other than those desired. The greater the number of genes that have to be inserted, the greater the risk of disruption to natural genetic functioning. There are additional difficulties that result from this type of metabolic tinkering: energy for the production of beta carotene may be diverted from other metabolic pathways in the plant, for example; or there is the possibility that the newly introduced enzymes in the plant may act in ways other than expected. Vitamin A rice is still at the developmental stage, and there is as yet little information on its composition, but it illustrates the greater potential for unexpected compositional changes that the next generation of GM crops are likely to present.

Establishing the effects of novel genes

Molecular analysis techniques, such as 'southern blot' analysis, are used to detect the presence of the inserted novel gene in the genetically modified organism. They can also be used to give an indication of where the novel gene is located in the genome of the host organism. Where the inserted novel gene has ended up determines whether or not it will have a disrupting effect on native genes in the plant and so, as was noted in a 1998 report for the Dutch Government: "[M]olecular analysis may provide information on the site of insertion of DNA constructs, but knowledge on DNA sequences of plants is still too limited to be of use for assessing possible side effects of the insertional events."²¹ While gene maps for the major crops, such as rice and maize, are close to completion, understanding of what the genes do and how they interact will take many more years to establish. In the absence of such information the real impact of putting new genes into an organism cannot be known. If, as the Dutch report suggests, knowledge is still too limited to be able to establish whether or not there may be side effects, then perhaps we should consider whether the whole push for commercial GM crops is premature.

In addition, it is becoming apparent that the techniques used for analysing the GM crops already on the market did not provide full or accurate information about inserted genes. For example, in 1996 Monsanto submitted its safety assessment of GM Roundup Ready soya 40-3-2 to the UK's Advisory Committee on Novel Foods and processes (ACNFP). In this, Monsanto provided information about the number of novel genes inserted and where they were located in the plant's genome, but no information could be provided about the function of the native genes surrounding the novel gene, and whether these native genes were functioning as normal.²² In 2000, Monsanto produced an additional molecular characterisation report on its GM Roundup Ready soya 40-3-2. This still could not address the issue of effects on neighbouring genes, but it did show that Monsanto's original analysis was not complete. The analysis conducted in 2000, which used newer techniques, found that two sections of DNA (fragments of the glyphosate tolerance gene CP4 EPSPS) had been inserted into the GM soya but that these were not detected in the original analysis.²³ The UK's ACNFP declared

that these extra pieces of DNA were not of concern in the case of Monsanto's GM soya, but even fragments of DNA inserted into the organism could have an impact upon genetic function. All of the GM crops already on the market were analysed using the same techniques that Monsanto was using in 1996. But to date, no other company has come forward with a new analysis of its GM crop.

More sensitive techniques need to be developed and applied to the molecular analysis of GM crops and foods. It is essential that the first step in the safety assessment of GM organisms should be to establish whether or not the inserted novel gene is having an effect upon the host's genetic functioning. For example, researchers from the Netherlands have developed a technique for the analysis of mRNA,²⁴ which is the messenger that a gene sends out into the cells of an organism. Analysis of the amount and type of these messengers could be used as a screening method for detecting any unexpected changes in genetic functioning caused by a gene insertion. Serious changes could then be investigated further - such a technique would provide a far better method for establishing how close a GMO is to the original organism. Analyses such as this, and those conducted by Monsanto on their GM soya, should be applied across the board. What further information would result if such sensitive analyses were conducted on all the GM crops that have been released onto the market?

Markers for novel genes

Whatever means is used to genetically modify a plant cell, the success rate is very low and it is necessary to have a means of identifying those cells which have been successfully modified from the rest of the cells which have not. This is done by use of a marker gene, which is attached to the novel gene, and which confers a characteristic that is easily tested for. The addition of a gene for the production of β glucuronidase (which produces a blue colour), for example, would allow the transformed cells to be selected visually.²⁵ However, one of the most common techniques so far has been the use of antibiotic resistance genes. In this case, the transformed cells gain resistance to a specific antibiotic, so that when it is applied the transformed cells survive while all the others are killed. However, these marker genes are usually retained in the plants after they are developed for use as a food crop, and this has been a source of continuing controversy.

Antibiotic resistance

The biggest concern about antibiotic resistance markers (ARMs) is the possibility that they could be transferred to bacteria in the guts of animals or humans, or to bacteria in the environment. Many bacteria have the ability to pick up genes from their surroundings and to pass these genes on to other species of bacteria, including those which cause disease. There is a danger therefore that diseases could become resistant to important antibiotic drugs. The British Medical Association has stated that: "The BMA believes the use of antibiotic-resistant marker genes in GM foodstuffs is a completely unacceptable risk, however slight, to human health."²⁶ In its report on GM foods, the House of Lords Select Committee on the European Communities recommended that antibiotic resistance marker genes "should be phased out as swiftly as possible"²⁷. The British Medical Association recommended in its report on GM

crops and food that “there should be a ban on the use of antibiotic resistance marker genes in GM food”²⁸. The use of antibiotic resistance genes has also been criticised by the Royal Society, the UK Government’s Advisory Committee on Novel Foods and Processes²⁹ and the National Farmers Union³⁰. In contrast, the US FDA has remained unruffled about the presence of antibiotic resistance markers in GM foods and, by the time it produced guidance on the subject in 1997, it had already approved 19 GM crops containing one or more antibiotic resistance marker genes.³¹

Marker genes giving resistance to the same antibiotics appear in a wide range of crops. For example, the *nptII* gene gives resistance to the antibiotics neomycin, gentamycin B and kanamycin. It is argued that the use of this marker gene is not worthy of concern because many bacteria in the environment already have resistance to these antibiotics. However, it does not seem prudent to have this gene in all of the following GM crops: Bejo Zaden’s herbicide-tolerant chicory; Zeneca’s delayed ripening tomato; Calgene’s high laurate oilseed rape; DNA Plant Tech’s delayed ripening tomato; Monsanto’s insect & virus-resistant potato lines; Monsanto’s delayed ripening tomato; Agritope’s modified ripening melon; Monsanto’s insect-resistant & glyphosate-tolerant maize; Plant Genetic Systems’ GM herbicide tolerant oilseed rape; Pioneer Hi Bred’s MON 809 maize. All of these are approved for use in food in the US. In contrast, only the processed products of the last two have been approved for food use in the EU.

The biggest concern lies with *ampR* marker gene, which confers resistance to antibiotics in the ampicillin family. This gene is found in Novartis’ insect-tolerant Bt 176 maize and Aventis’ T25 herbicide-tolerant maize (although only partial copy of the gene is present) which are approved for use in food and animal feed in the EU and the US. The gene is also in Aventis’ T14 herbicide-tolerant maize, Dekalb’s DTB418 maize and Dupont’s high oleic acid soybean which are only approved in the US. Novartis’ Bt176 maize is grown in Spain and Portugal.

When the UK’s Advisory Committee on Novel Foods and Processes (ACNFP) assessed Novartis’ Bt 176 maize, it noted that the gene was associated with a bacterial ‘origin of replication’. In bacteria, the origin of replication controls how many copies of the gene they can produce - the more copies of the gene there are, the more protein is produced and so the greater the power of the bacteria to resist the ampicillin antibiotics. The origin of replication in Novartis’ maize was artificially constructed and is not found in nature. It would allow bacteria to produce more than 600 copies of the antibiotic resistance gene. The naturally occurring version would only allow them to produce between four and 18 copies. This means that if bacteria acquired these genetic constructs from the Novartis maize, they would become resistant to the antibiotics in the ampicillin family. The ACNFP realised that if this gene were taken up by bacteria, it “would lead to more rapid degradation of ampicillin and other β -lactam antibiotics by cells containing [this gene] than by those found in the natural environment”.³² In other words, it would allow bacteria to break down these antibiotics much more rapidly than they could otherwise.

The ACNFP has also expressed concern that the parental gene of *ampR* commonly mutates, with the mutations extending the range of antibiotics against which it confers resistance.³³ This could include the ‘last defence’ cephalosporon antibiotics. One member of the committee said in 1999 that “were such mutated genes to develop in transgenic plants, and were they to find

their way from plants back into the microbial gene pool, the consequences could be grave”.³⁴ In this case, the ACNFP was so concerned that it recommended the gene be removed before the maize was allowed to enter the food chain. The committee was particularly concerned that the resistance gene could be transferred to bacteria in the guts of livestock, and from there be passed to bacteria which cause disease in humans.³⁵ The committee’s concerns were shared by the regulatory authorities around Europe and eventually 13 out of 15 member states proposed to refuse European marketing approval for Novartis’ maize. Despite this, in 1996 the European Commission overruled the member states and approved the crop.

Most GM food for humans is highly processed. Processing tends to break down the DNA in food, making it less likely that bacteria would be able to pick up ARMs from GM food. However, animal feed is much less processed and this may be a route for the transfer of GM antibiotic resistance genes into bacteria in the food chain. Whilst this caused concern to the UK Government’s scientific advisors, it appears to have been taken far less seriously by the companies producing these crops. For example, maize is commonly made into silage by being partially fermented in a store and then fed to cattle. In 1996, Sharpes International Seeds made an application to the UK Government to release Aventis’ T14 GM maize, (which contains the ampR gene).³⁶ The ACNFP expressed concern to the company about the possibility of this gene being passed to cattle from the GM silage. In their response, Sharpes merely stated that in the opinion of their “specialist colleagues” this was “impossible”.³⁷ No evidence was provided to support this statement. Later, a report commissioned by MAFF found that specific genes could easily be extracted from maize silage. This type of research should be conducted by companies before they make statements about the safety of their products. In fact, the MAFF-sponsored researchers concluded that: “Our results clearly showed that DNA remained stable in silage and so, if there is a significant risk of transmitting a transgene in the gut of farm animals, it would seem sensible not to use ensiled GM crops as animal feed.”³⁸

The British Medical Association has warned that: “The risk to human health from antibiotic resistance developing in micro-organisms is one of the major public health threats that will be faced in the 21st Century.”³⁹ Although the contribution of marker genes in GM plants to this is still a matter for debate, it should be remembered that bacteria known to be capable of taking up and expressing free DNA includes *Neisseria meningitidis*, which causes meningococcal meningitis, and this mechanism has been suggested as the means by which the gonorrhoeae bacteria *Neisseria gonorrhoeae* became resistant to penicillin.⁴⁰ As the UK ACNFP noted in a letter to the US FDA, while risks to healthy adults might be low, “transfer of resistance genes may pose a much more significant threat to the very young, the elderly and those people who are immunocompromised”.⁴¹

There is as yet no direct evidence of this transfer from GM food to gut bacteria. However, unpublished research at the University of Jena in Germany found gene transfer from genetically modified rape pollen to bacteria in the intestinal tract of bees.⁴² Obviously this research needs to be confirmed, and the intestinal tract of insects is significantly different to that of mammals, but this may well indicate that gene uptake by competent bacteria is a real possibility. Researchers in the UK have found that bacteria in the mouth are capable of taking up and expressing naked DNA from saliva,⁴³ so it is possible they could incorporate genes from GM food when it is eaten. In the Netherlands, researchers used a model of a human gut to look at what would happen to GM food after it is eaten. They predicted that six per cent of

the genes from GM tomatoes would survive digestion⁴⁴ and considered that the genes could survive for long enough for bacteria to pick them up. It has even been suggested that bacteria in the respiratory tracts of workers could pick up DNA from pollen or flour during production and processing of GM crops.⁴⁵ Although the relative frequency of such events is likely to be low, the ACNFP has pointed out that “given the huge amplification of resistance genes implicit in the agricultural application of transgene technology, even rare events will happen”.⁴⁶

3. *Substantial equivalence*

Over the last ten years there has been a succession of serious incidents affecting public health that were brought on by changes in food production. Examples include the rise of salmonella infection in UK poultry flocks to epidemic levels, the rise in E coli 0157 poisoning around the world, and of course bovine spongiform encephalopathy (BSE) in UK cattle and the subsequent development of new variant Creutzfeld Jacob Disease in humans. All these incidents have made it increasingly clear to consumers that, in a world where food production operates on large scales and is widely industrialised, small changes can lead to disastrous consequences. Researchers in the UK found that consumers viewed food safety issues as long-term and complex, and that on such issues “studies would have to be undertaken for many years, maybe even a generation, before people would be convinced”.⁴⁷ And, while the biotech industry has consistently claimed that GM foods are as safe as any other, government regulators have put in place procedures for examining the safety of GM crops and foods. In recent years, a heated debate has developed about their effectiveness and appropriateness. In particular, attention has focused on the concept of substantial equivalence, upon which much of the assessment procedure is based. This chapter examines the concept, and its appropriateness as a tool for examining the safety of GM crops.

Substantial equivalence

Since the early 1990s, various international industry and governmental organisations have worked to design strategies for evaluating the safety of GM foods, including the International Food Biotechnology Council (IFBC)⁴⁸, the Organisation for Economic Cooperation and Development (OECD)⁴⁹, the United Nations Food and Agriculture Organisation (FAO)⁵⁰ and the World Health Organisation (WHO). Although these strategies have not had legal status, the principles evolved have been incorporated in varying forms into national legislation. The common methodology for these different strategies and national legal requirements has been a comparison between the GM food and a non-GM counterpart. The underlying rationale for this comparative assessment (rather than a safety assessment of the GM food in isolation), is the assumption that existing foods have a long history of safe use and so, if a GM crop is found to be the same as the non-GM counterpart, it too should be able to lay claim to this history of safe use. This approach, referred to as substantial equivalence, has come to underpin the safety assessments of GM foods around the world.

Testing problems

Substantial equivalence was developed as a response to the difficulties encountered when standard procedures, used for testing the safety of single chemicals, were applied to foods. All foods are made up of a complex mixture of different compounds, which provide their energy and nutritional value. They contain beneficial nutrients, such as protein and starch, which provide the major nutritional value, as well as vitamins and minerals. But they may also contain compounds which are not beneficial, ranging from the caffeine in tea and coffee to the poisonous glycoalkaloids present in green potatoes. Foods may also contain anti-nutritional

compounds, such as phytate in wheat which prevents the absorption of iron, or they may contain allergens like those in peanuts. It is the combination of all these components which determines the safety and nutritional value of a food and its products, and genetic modification has the potential to affect any of these. This complexity made the existing toxicological techniques used for single compounds extremely difficult to apply.

Procedures for testing the safety of new chemicals and medicines have been in use for decades. However, these were developed to examine the safety of a single compound, not for testing a range of compounds which will all be eaten at once, as is the case for GM foods. It is extremely difficult to isolate the effect of any one compound in a food, and impossible using the techniques available at the beginning of the 1990s to look at the effects of all the different compounds in GM food at the same time. For example, a fairly crude safety test for any compound is the high dose feeding trial. In the test, rats or mice are fed higher and higher doses of a new drug, food additive or chemical, until a toxic effect is observed. This is supposed to provide a starting point for the examination of the nature and level of any toxic effects. But even this crude examination cannot be applied to GM foods. For example, in one study freeze-dried GM tomatoes were fed to rats, at a rate equivalent to 13 fresh tomatoes per rat every day⁵¹. But even this incredibly high dose was still not enough to satisfy the dosage requirements normal for a single compound. It was simply not possible for the rats to eat enough tomatoes and, even if they could have done so, their diet would have been so unbalanced that this alone would have made them ill.

While the methods used for food additives and medicines turned out to be largely inapplicable to whole foods, historically there were few attempts to assess the safety of conventional foods. This meant that there was no experience upon which to draw and a huge gap was found between the ability to create GM foods and the ability to test their safety. This was recognised by the scientists at the OECD and the WHO was charged with coming up with procedures for assessing GM food. But instead of taking the clear, strong position of pointing out that there was no adequate way to assess the safety of GM foods, the WHO compromised and came up with substantial equivalence. The safety of non-GM foods is based largely upon their history. It is generally accepted that if there is a history of safe use for a food, such as rice, wheat or potatoes, then the food is safe for most of the population. The scientists reasoned that if a GM food could be shown to be the same as a conventional food, it would also be able to lay claim to this history of safe use. The problem with this was that GM foods, most of which contain compounds that have never been eaten before, are never entirely the same as a conventional food.

To solve this contradiction, it was decided that only a degree of 'sameness' would be required. What degree of sameness would suffice remained uncertain and so it was decided GM food would be allowed to lay claim to the safety of a normal food, if it was shown to be mostly the same as its conventional counterpart - if it was substantially equivalent to it.

In 1994, the OECD developed the methodology that underpins GM food safety assessment in the industrialised nations,⁵² and it based this on the concept of substantial equivalence. It established the principle that the greater the equivalence of a GM food to its conventional counterpart, the smaller the requirement for testing. So the EU Scientific Committee for Food has since recommended the following:

“In establishing the need for the provision of toxicological data, three scenarios may be considered:

(1) Substantial equivalence can be established to an accepted traditional food or food ingredient, in which case no further testing is needed.

(2) Substantial equivalence can be established except for a single or few specific traits of the NF [novel food], in which case any further assessment of safety should focus specifically on these traits.

(3) Neither partial nor total substantial equivalence can be established; in this case, the wholesomeness of the whole novel food or macronutrient has to be assessed using an appropriate combined nutritional-toxicological approach.”⁵³

Familiarity

The premise which forms the bedrock of substantial equivalence is that we fully understand conventional foods. If we have familiarity with normal foods, we should be able to spot any differences in GM foods and work out whether or not they are harmful. Yet it is clear that there are vast areas of ignorance about the safety of foods and their impact on our health. A long history of use of a food does not guarantee real familiarity, at least not familiarity with relevant issues. Food safety concerns, for example, have tended traditionally to focus on issues of contamination, such as disease causing bacteria or industrial chemicals, rather than on the safety of the foods themselves. This means that there are a wealth of techniques for detecting food contaminants, as well as good understanding and extensive legislation, but little of any of these exist for the uncontaminated foods themselves. A comparable problem occurred during the examination of the environmental impacts of GM crops. Austrian researchers looking into this problem found that in many cases it was extremely difficult to make comparisons between GM and conventional crops because “in practice, ‘familiarity’ with a certain crop plant refers primarily to agronomic performance and less to environmental impacts”.⁵⁴ In other words, the aspects of agricultural crops for which there is extensive background information, such as yield or disease resistance, are not relevant when conducting an environmental impact assessment. The same may well be true with foodstuffs, and it should not be assumed that a long history of use of a food implies an understanding of the issues that are relevant when considering the impact of genetic modification.

Problems of definition

What actually constitutes a substantial degree of equivalence between a GM and a non-GM food has never been clearly defined. Without quantification this is still a matter of discussion and debate. Apparently, it is not clear either to regulators or the industry exactly what level of sameness is considered to represent substantial equivalence, nor how this should be measured. The issue inevitably becomes a matter of opinion:

- In 1996, Monsanto published compositional analyses of its GM Roundup Ready soybeans in comparison with a non-GM control variety of soybean. Only a small number of samples were used, but the results still showed statistically significant differences in ash (carbon), fat and carbohydrates content between the GM and non-

GM soybeans. However, the authors commented that they considered the measured differences to be “biologically unimportant” and that “the analytical results demonstrated that the GTS [glyphosate-tolerant soybeans] are equivalent to the parental, conventional soybean cultivar”.⁵⁵

- In contrast, in 1999 an examination of phytoestrogen content in Roundup Ready soya found a statistically significant reduction of levels in the GM soybeans in comparison with the non-GM counterpart. The authors stated that they considered that “these data suggest genetically modified soybeans may be less potent sources of clinically relevant phytoestrogens than their conventional precursors”.⁵⁶
- In 1996, Aventis (then AgrEvo) submitted an application for marketing consent under EU Directive 90/220/EEC for its GM T25 maize. In this, Aventis’ own analyses of T25 maize grown in the US found significant differences in fat and carbohydrate content between the GM and non-GM maize grains.⁵⁷ In addition, a more detailed analysis found statistically significant differences in the levels of three amino acids (arginine, histidine and lysine) and three fatty acids (stearic acid, linoleic acid and arachidic acid).⁵⁸ In a separate document, submitted to ACNFP, Aventis stated that the levels of linolenic and arachidic acid were outside the range of values reported in any other study.⁵⁹ Despite these findings, the company claimed that: “Analyses showed that GTC [glufosinate tolerant corn] silage and grain are not materially different from current commercial varieties in essential nutrients or antinutrients.”⁶⁰
- Dr Vyvyan Howard, Head of the Fetal and Infant Toxicology-Pathology Group at the University of Liverpool, and a Fellow of the Royal College of Pathologists, examined this evidence for Friends of the Earth. He was particularly concerned about the differences observed during the amino acid analysis, commenting that the “three amino acids are similar in chemical composition, possessing an additional NH₂ group. No further analysis was made into this difference, despite the fact that the introduced PAT-protein is an N-acetyl transferase, an enzyme that might be expected to react with such molecules. It is possible that the increased levels of these three amino acids are connected to the introduction of the PAT protein”.⁶¹ Examining the documents submitted to the UK’s ACNFP by Aventis, he commented that: “The final conclusion is that T25 maize is not “materially different” from current commercial varieties. However the measurements made suggest a different conclusion.”

The minutes of an OECD-organised meeting of GM regulatory authorities from around the world held in Paris in 1998, show that even by then there was still not a common understanding. The UK delegation proposed a plan for the statistical requirements for the assessment of the substantial equivalence of GM foods. The following comments from other countries were minuted in response:

“What will be the impact of the approach on interpretation of data – how will a significantly different result (from the control crop) be interpreted in the context of the safety of the crop – if a result was still in a historical range what would happen – more components, more samples?”⁶²

By the end of 1998, when 40 GM foods had been approved for use in the US, and GM soya and maize were on sale in the EU, the regulatory authorities were still not clear what would constitute scientifically sound and valid data to support an assessment of whether or not a GM crop was substantially equivalent to its conventional counterpart. As far as FOE is aware, the OECD is still attempting to develop guidance on this issue and so, as was noted in 2000 by the Italian Ministry of Health, “substantial equivalence remains a concept which is scientifically ambiguous”.⁶³

Worldwide interpretations

Substantial equivalence is a compromise, developed as a result of the inability to really measure the safety of GM foods. But this compromise is prone to difficulty - it is so unclear, so open to interpretation, and can therefore be applied in many, starkly different ways. Which is exactly what has happened - a substantial equivalence judgement means one thing in the US and quite another in the EU.

In the EU, the issue of what constitutes a substantially equivalent GM product was not finalised until fairly recently. The EU operates a dual safety assessment procedure for GM foods, with those deemed to be substantially equivalent requiring far less consideration by member state governments.⁶⁴ A definition of what constituted substantial equivalence was required in order to operate this system. Eventually, after a meeting of the GM food safety assessment authorities from around Europe, it was agreed that a GM food could only be considered to be substantially equivalent to a non-GM food if it did not contain any GM DNA or protein, and showed no other differences in composition.

The US position is almost exactly the opposite. The US FDA produced a policy document on the safety assessment of GM foods in 1992,⁶⁵ in which it was stated that GM foods would be exempt from pre-market safety testing if they were considered to be the same as existing food products, or ‘Generally Recognised As Safe (GRAS)’. The FDA stated, with respect to GM DNA: “Generally, FDA does not anticipate that transferred genetic material would itself be subject to... regulation... In regulatory terms, such material is presumed to be GRAS ... The FDA expects that the intended expression product or products present in foods derived from new plant varieties will typically be proteins or substances produced by the action of protein enzymes, such as carbohydrates and fats and oils ... minor variations in the molecular structure that do not affect safety would not ordinarily affect the GRAS status of the substances.”

So, while the EU has determined that GM proteins or DNA cannot ever be considered to be substantially equivalent to a non-GM version, the US presumes GM DNA and protein are substantially equivalent unless shown otherwise.

This has led to the bizarre situation in which whole crops have been deemed as being GRAS - substantially equivalent - in the US, while only highly processed derivatives of these crops are approved as substantially equivalent in the EU (see Table). In addition, the Italian Government has ruled that even those maize products approved in the EU are not necessarily substantially

equivalent.⁶⁶

Substantial equivalence in the EU and US

Company	GM crop	US GRAS ruling	EU decision on substantial equivalence
Aventis	glufosinate-tolerant oilseed rape lines (canola)	whole crop approved	processed oil only
Plant Genetics Systems	glufosinate-tolerant oilseed rape lines (canola)	whole crop approved	processed oil only
Monsanto	glyphosate-tolerant oilseed rape (canola)	whole crop approved	processed oil only
Monsanto	'Bt' insect-resistant maize	whole crop approved	flour, gluten, semolina, starch, glucose & oil only*
Aventis	glufosinate-tolerant maize	whole crop approved	starch, oil and heat processed/fermented products only*
Novartis	'Bt' insect-resistant maize	whole crop approved	'food & food ingredients'*
Pioneer Hi Bred	'Bt' insect-resistant maize	whole crop approved	'food & food ingredients'*
Dekalb Genetics	glufosinate-tolerant maize	whole crop approved	not substantially equivalent [†]
Monsanto	'Bt' insect-resistant potato	whole crop approved	not substantially equivalent [†]
Monsanto	'Bt' insect-resistant & glyphosate tolerant maize	whole crop approved	not substantially equivalent [†]

* Under challenge from the Italian Government which argues that these products do not qualify as being substantially equivalent under the terms of Article 5 of the Novel Foods Regulation 258/97.

[†] Decision by the UK competent authority for GM foods (Advisory Committee on Novel Foods and Processes)

Future foods

The next generation of GM foods will have no equivalent. For example, take the case of the recently developed beta carotene-producing rice. How will this be compared to non-GM rice, which does not share the metabolic pathway that produces beta carotene? The greater the difference between the GM crop and its non-GM counterpart, the more difficult the concept of substantial equivalence becomes. The EU Scientific Committee for Food attempted to tackle this problem by suggesting that the assessment “contains a dynamic element, as the continuing modification of a food requires that the basis of comparison will evolve in a way that the most recent NF [Novel Food] is compared with an appropriate former NF and not necessarily with the most traditional counterpart”.⁶⁷ In other words, as GM crops and foods become more different from conventional ones, their substantial equivalence should be assessed against existing GM crops and foods. This proposal does little to solve the inherent difficulties of substantial equivalence, but does raise the possibilities that any mistakes made with one generation of a GM crop could be compounded in the next. The idea that a new GM food would be deemed to be acceptable because it is substantially equivalent to a GM food that was substantially equivalent to a non-GM food does not provide much comfort.

Dr Andrew Chesson, who is a senior scientist at the Rowett Research Institute and a member of one of the EC’s scientific advisory committees, gave evidence to the UK Government’s Select Committee on Science and Technology in 1999. He said then that he had concerns about the use of substantial equivalence to assess the next generation of GM crops: “We are looking at such a very large, potential range of transgenic crops and foodstuffs in the future that I think the whole concept, the framework, of substantial equivalence will assume increasing importance. And used in the way that it is currently used, I do not think it will necessarily be adequate for that purpose.”⁶⁸

A recent report by the Royal Society of Canada concludes that “the use of substantial equivalence as a decision threshold by regulatory agencies is, in the Panel’s view, scientifically unjustifiable when used to exempt new products from full scientific scrutiny”. The report went on to say that approvals of GM food or feed “should be based on rigorous scientific assessment of their potential for causing harm to the environment or to human health. Such testing should replace the regulatory reliance on substantial equivalence as a decision threshold”.⁶⁹

Developing countries

The issue of substantial equivalence and how it affects food safety is of even greater importance for developing countries. Rich people’s diets are usually varied - it is unlikely that one single food will make up a large percentage of the diet. But for the poor, diets are restricted by what is affordable, and a single food can make up an extremely large proportion of the diet. A report by the UN FAO found that maize provides up to 45 per cent of the daily calories and 59 per cent of the daily protein for both rural and urban populations⁷⁰ in Central America.

It is widely proposed that GM crops be introduced in developing countries to feed the poor.

This would mean that GM foods would make up an excessively large proportion of the food of the poor.

It is comments made by the US Government with respect to their animals that are probably of most relevance in this case. The Director of the Centre for Veterinary Medicine stated that GM crops would be of particular concern for livestock because “a single plant product may constitute a significant portion of the animal diet. For instance, 50-75 per cent of the diet of most domestic animals consists of field corn. Therefore, a change in nutrient or toxicant composition that is considered insignificant for human consumption may be a very significant change in the animal diet”.⁷¹ If this argument is valid for US cattle, what about humans? If a GM maize replaces the staple maize crop, what will be the impact of the “changes in composition” found in several GM maize lines?

There is already evidence that ‘green revolution’ crops - introduced in the 1960s and 1970s as a solution to world hunger - have caused themselves problems due to their changed nutrient composition. High-yielding green revolution crops have been found not to take up essential minerals from the soil, so that when the proportion of calories provided to people by these crops rose, their intake of key micro-nutrients fell. A recent report by the Global Environmental Change programme suggested that one quarter of the world’s population is now affected by “green revolution iron deficiency”.⁷² The report claimed that such deficiencies have led to impacts on the brain and intelligence in the populations of many developing countries. As it is the poor who have these staple foods as the largest proportion of their diet, they suffer most from these effects. In the long term it is to be hoped that these inequalities will change, but as things stand, for poor people it is more important that the foods they consume are safe, as they will have little with which to vary their diet and dilute possible effects.

If GM crops are to ‘feed the world’, they must be subject to the most stringent safety testing. Monsanto and Aventis have used substantial equivalence to argue that significant differences in composition are of little importance in the diet as a whole. But this is not an appropriate way to assess the safety of GM foods for the world’s poor and vulnerable.

4. Establishing the safety of GM foods

“So basically it’s a cop out. If somebody did fall ill in five years from then, he would then have a get-out and be able to say: ‘but I said there was no scientific evidence of that. I didn’t say it couldn’t happen’.”

Interview with a Lancashire mother about the regulation of GM foods, 1996⁷³

Unexpected effects

One of the most commonly voiced concerns about the safety of GM foods is the possibility that changes in nutritional value, or even toxic effects, will be produced in the GM food as an unexpected consequence of genetic modification. Establishing the substantial equivalence of a GM crop or food is reliant upon being able to identify any changes that might have occurred. At the moment, tests only look at what is already known to be present in the food. They measure the levels of individual, known components, such as protein, starch or fat, to see if there is any change. This cannot detect anything new or unexpected. As a recent OECD report on the safety testing of GM foods pointed out, “analysis based on single compounds as a screening method for unintended effects of genetic modification, has its limitations with regard to (unknown) anti-nutrients and natural toxins”.⁷⁴ As was also noted in the OECD report, information about the interactions of the many different compounds found in food is limited and inevitably leads to problems in analysing the results.

Often there is only limited information on what constitutes a normal level of naturally occurring toxins. This means that there is a limit to any understanding of what the impacts that a change in the levels of any one of the many compounds found in foods might have in terms of food safety. In the most common approach, levels are deemed acceptable if they fall within the range of values published in the literature for all the varieties of that particular crop grown around the world. But there is no scientific basis for this as a definition of safety. Indeed, it is not even clear whether such information is reliable. When discussing this kind of data at an OECD meeting, it was noted that “the quality and level of this information was variable and did not always inspire confidence”.⁷⁵

A recent study by the University of Vienna analysed notification documents submitted to the EU and US Governments in support of GM varieties of oilseed rape, maize, tomato, potato and soybean.⁷⁶ The researchers specifically examined the consideration of naturally occurring plant toxins in the crops, and whether the companies had checked the levels of these after genetic modification. They found that “in several documents used for notifications no declarations even on essential inherent plant toxins and antinutrients could be found”. For example, out of four notifications for GM maize, only one examined the levels of the anti nutrient phytate, which hinders absorption of iron. While the authors support the continued application of substantial equivalence, they still noted that “consistent guidelines, specifying data of relevant compounds which have to be provided for notification documents of specific organisms have to be established”.

For the vast majority of foods, even those which are eaten widely throughout the world and regarded as staples, understanding of the impact of the food and its constituents on health is fairly limited. This leads to difficulties when assessing any changes to a food caused by genetic modification. For example, in a report produced by the ACNFP on insect-resistant maize it was stated that “there are no inherent toxic or antinutritional factors present in maize”.⁷⁷ Yet recently it has been suggested that linoleic acid, which is a major fatty acid of maize, may be linked to immune system suppression when it forms a major part of the diet, as is the case for many poor people in developing countries.⁷⁸ The extent of this effect is still unclear, but changes in linoleic acid content which have previously been considered to be insignificant could have a serious impact in those areas where maize is a staple food. Changes in fatty acid profiles, including linoleic acid content, have been found in GM maize varieties produced by AgrEvo, Monsanto and Pioneer Hi Bred (see Chapter 2).

Don't look - don't find

One of the most serious failings of the current approach is that simple composition analysis is unlikely to detect unexpected or unintended impacts of genetic modification. In most cases, analysis of this sort relies on knowing what to look for. Obviously, an examination that focuses only on known substances will not reveal unknown substances that may have toxicological relevance. In 1999, the Rowett Research Institute (RRI) presented evidence to a UK Government investigation of GM crops and foods.⁷⁹ Several senior staff at the RRI have been involved in the scientific assessment of GM foods and crops, both at the UK and EU level. In a memorandum submitted by the RRI to the investigation, it is stated that:

“Much of the data produced is simply a measure of gross composition which is difficult to interpret. At what levels do changes to protein, carbohydrate or fat concentrations pose an additional risk to human health and why? There is obvious value in measuring the concentrations of known natural toxicants such as glycoalkaloids in potato or glucosinolates in brassicas, since safe levels for these compounds have been established. The routine analytical procedures currently used, however, would be unlikely to detect toxic metabolites which accumulated because the introduction of transgenic material silenced an existing plant gene and disrupted a metabolic pathway. The concept of substantial equivalence would be better served by the use of techniques which make no assumptions but which attempt to measure the construct as a whole.”⁸⁰

The Institute suggested that more appropriate approaches for establishing the likely effects of genetic modification would be the use of techniques which investigate changes in the activity of genes and total protein expression in the organism, as well as an analysis of the metabolism of the GM plant to see if any unexpected changes had occurred to metabolic pathways. Techniques to aid such an analysis are being developed, and work is underway to establish techniques for analysing food compounds using methods such as liquid chromatography, mass spectrometry and nuclear magnetic resonance imaging.⁸¹ These techniques can be used to establish a chemical fingerprint for the GM food and this can be compared with the conventional counterpart. Such techniques are much more sensitive than simple chemical analyses and can detect tiny differences in the overall composition of foods. These sensitive

techniques are far more likely to pick up unknown toxins or other chemicals in the GM food, but they are still at an early stage of development.

More sensitive testing is essential if companies want to introduce GM foods into our diets. There is still the obvious problem of interpretation, but at least this would be a better starting point than what we have at present. Better methods are being developed, and yet nothing has changed for those GM foods that have already been approved, or are waiting for approval for food use. After their investigation into the assessment of GM foods, the UK Government's Select Committee on Science and Technology commented that "any robust and sustainable scientific advisory system must be prepared to challenge some of its basic tools".⁸² Much better analyses must be applied to all GM crops, particularly those that we are already eating, because we need to know exactly what is in the GM food on the market at the moment, as well as what might appear in the future.

Appropriate testing

"Another consideration, in determining the need for animal studies, is whether it is appropriate to subject experimental animals to such a study if it is unlikely to produce meaningful information."

OECD Task Force for the Safety of Novel Foods and Feeds, 2000.⁸³

At the moment, companies often use animal tests to provide support for claims about the safety of their GM foods. Most commonly, these consist of short-term toxicity studies using the novel protein which has been extracted from the GM food. This is done because companies usually claim substantial equivalence for their GM crop apart from the novel protein, and this alone is then subjected to toxicological testing. In addition, there are real difficulties in conducting toxicity tests using whole foods (see Chapter 3), but even so, some companies conduct short-term feeding trials using the whole GM crop or food. These are commonly referred to as wholesomeness or nutritional studies rather than toxicological assessments.

The way in which such tests are applied can hugely affect whether any useful information is obtained. For example, Northrup King and Monsanto have both used the same high-dose feeding study on mice to justify the safety of the CryIA(b) insecticidal toxin. This is naturally produced in the bacterium *Bacillus thuringiensis* (Bt) and, through modification, is also produced in the GM maize lines.⁸⁴ This study has never been published or subjected to scrutiny by peer review. In the test, ten mice were given an enormous dose of the bacterial toxin and observed for two weeks for any signs of adverse effects. However, because the Bt toxin is produced at low levels in the GM plants and is difficult to extract, the test in fact used Bt toxin produced and extracted from genetically modified bacteria. There are several failings with this approach. Firstly, people eating the GM foods will be eating the Bt toxin at low doses over a long period, rather than as a single huge dose. In addition, it is entirely possible that the Bt toxin produced in the GM maize could be different from that produced by GM bacteria, due to the uncertain effects of gene splicing. Finally, the technique was criticised by

the EU Scientific Committee on Plants because “the use of the isolated protein in toxicity studies does not adequately model degradation of the same protein when fed as an integral component of the diet”.⁸⁵

In similar tests, Novartis conducted two-week acute toxicity studies with mice using CryIA(b) toxin taken from the bacterium *Bacillus thuringiensis* and from their own Bt 176GM maize. They also conducted acute toxicity studies using Bobwhite quail (*Colinus virginianus*)⁸⁶. Novartis has claimed that neither study showed any negative effect from the Bt toxin produced in their GM crop. However, these studies have never been published and, despite repeated requests by Friends of the Earth, Novartis has consistently refused to make any results from them public.

According to the companies, these unpublished studies indicate that there is no reason to be concerned about Bt toxins in GM crops and food, but the published literature at least points to a different conclusion. For example, in 1998 researchers at an Egyptian university found that both naturally occurring CryIA(b) Bt toxin and one introduced through genetic modification into a transgenic potato caused damage to the cells lining the small intestine.⁸⁷ Although the damage to the small intestine was worse in those mice fed the unmodified Bt toxin, the authors of the study recommended that similar tests should be conducted on all GM crops containing the Bt toxins, in order to assess their safety. As can be seen from the table below, biotech companies have not engaged in this kind of specific, targeted safety testing. In a more recently published paper examining the immunological impact of Bt toxins, it was found that the CryIA(c) toxin produced an immune response in mice after they were fed it.⁸⁸ The authors concluded that “the high immunogenicity of CryIA proteins administered ig [intra-gastric] should be taken into account before releasing Cry-containing products for human use”.

While Novartis and Monsanto have both conducted tests on the Bt toxin, there is no evidence that they examined the two areas where independent researchers have found cause for concern. When GM Starlink maize, containing the Bt toxin Cry9(c), was introduced into the US food chain by Aventis, a number of consumers reported allergic reactions. This is not surprising, considering there is only one published study examining the immune system response to these toxins, and that it stated: “Little is known about the physiological or immunological effects of the Cry protein family on vertebrate organisms.”⁸⁹ If companies continue to conduct inappropriate tests which they refuse to subject to peer review or even produce results from, this situation will not change. In the future, it is proposed that a wide range of novel proteins be introduced into GM crops, in which case, the biotech companies must make more than this desultory effort to assess their safety. Wasting the lives of animals in poorly conceived experiments is not acceptable, either for animal welfare or for protecting human health.

Feeding studies using the whole food are also problematic. As has been outlined earlier, independent scientists found that foods, which are bulky mixes of different compounds, are often impossible to feed to test animals in large enough doses to produce any meaningful result. In addition, a feeding study using large amounts of a single food is likely to so distort the diet that this alone could have health impacts.⁹⁰ However, if the whole food is fed at lower levels, there is little likelihood of detecting any but the most severe type of acute toxic effects. Such tests can contribute little to an understanding of the safety of GM foods. For example,

Monsanto has published the results of its wholesomeness tests on its GM Roundup Ready soya. In the test, GM soya made up five per cent to ten per cent of the diet of rats, 26 per cent to 33 per cent of the diet of poultry, 47 per cent of the diet of catfish and 10 per cent of the diet of cattle. The stated purpose of these trials was “to provide further support for commercial acceptance of this new soybean variety”,⁹¹ but with respect to safety, the authors could only state that “the animal feeding studies provide some reassurance that no major changes occurred in the genetically modified soybeans”.

There is only one published feeding trial using Novartis’ Bt-176 maize, which used broiler chickens.⁹² In this study the birds fed GM maize put on weight more efficiently from the grain they ate than those fed non-GM feed. However, the authors were unable to determine whether or not this was an effect of the GM feed or the experiment, and eventually concluded only that Bt 176 did not show any “deleterious effects”. This type of design and interpretation problem is exemplified in the following case.

A feeding trial was conducted on behalf of Aventis on its herbicide-tolerant T25 maize. In this 1996 study, the GM maize and normal maize were fed to broiler chickens as part of their diet for 42 days. Their growth and performance was then measured. The authors of the study concluded that, based on their results, the GM T25 maize was nutritionally equivalent to non GM maize.⁹³ This research was not peer reviewed or published, even though it was used to support Aventis’ application for marketing consent in the EU for T25 maize. In fact, Aventis only made the research publicly available in 2000. The summary results of this study show that twice as many birds died when fed the GM maize as when fed normal maize and that other characteristics, such as weight gain, were much more variable for the GM-fed birds than for those fed non-GM grain.

When scientists from Bristol University’s Department of Clinical Veterinary Science were asked to peer review this paper by Friends of the Earth, after it was made available to the public, they expressed serious concerns about the quality of the study.⁹⁴ They stated that too few replicates of the experiment had been conducted (four, as opposed to a minimum of 14), so that only a huge treatment effect would have been detectable. They commented that, “if one were seeking to show no effect, one of the best methods to do this would be to use insufficient replication”. They also commented that the statistical analysis was poor and that there was no positive control in the study, which is standard procedure. Despite this, there were findings in the study which they felt should have been investigated further. So, for example, “the trend for higher mortality in the GM-fed birds - ten birds as against five birds - is also suspicious... as for weight and other variables, it suggests either a fault in the study or a real effect of diet”. There were so many failings in this study that the Bristol University scientists concluded: “Put simply, this study as reported is inadequate in terms of providing any evidence or conclusions. It is not of a standard that would be acceptable for publication in a scientific journal.”

While credit must be given to Monsanto for publishing the results of its trials with GM crops, it is unclear what they contribute to the further understanding of the safety of GM foods. A more detailed approach for establishing the chronic effects of low-dose exposures to GM foods would be to undertake long-term, multi-generational feeding trials of GM feedstuffs to livestock. Ironically, such tests are already being unwittingly conducted on livestock in the US

and Europe, but in an entirely uncontrolled manner, with no means of establishing what the outcome might be. This is because GM crops are in the main used as animal feeds, and most farmers have no idea whether they are feeding their animals GM feed or not.

Tests conducted on the GM crops approved for food in the EU (as at March 2001)

GM crop	EU approval for use in animal feed	EU approval for use in human food	Safety tests used to support applications for approval
Monsanto Roundup Ready soybean 40-30-2	Approved under EU Directive 90/220/EEC Ref: C/GB/94/M3/1	Released onto the market prior to the introduction of EU novel foods regulation. So never formally assessed for food safety	Published acute toxicity study in mice using novel protein EPSPS PCP4. Published wholesomeness feeding trials (GM soya fed as part of diet): Four weeks - rats (processed & unprocessed soybeans) Six weeks - battery chickens Ten weeks - catfish Four weeks - dairy cows
Novartis' Bt 176 insect-resistant & glufosinate-tolerant maize	Approved under EU Directive 90/220/EEC Ref: C/F/4/11-03	Released onto the market prior to the introduction of EU novel foods regulation. So never formally assessed for food safety	Unpublished study for Novartis examining the degradation of novel CryIA(b) protein in simulated mammalian gastric fluid containing pepsin. No examination of breakdown in intestinal fluids. Detailed results withheld by company. Unpublished acute toxicity (single large dose) study using novel cryIA(b) protein. Ten mice, studied for 14 days and using CryIA(b) protein from BT bacteria and GM maize. Detailed results withheld by company. Unpublished acute toxicity (single large dose) study using novel cryIA(b) protein. Thirty young bobwhite quails (20 as controls), studied for 14 days using CryIA(b) protein from the GM maize. Detailed results withheld by company. Unpublished acute oral toxicity (single large dose) study of novel PAT protein in (unknown number) mice. Detailed results withheld by company.

GM crop	EU approval for use in animal feed	EU approval for use in human food	Safety tests used to support applications for approval
Aventis' glufosinate-tolerant oilseed rape Topas 19/2	Approved under EU Directive 90/220/EEC Ref: C/GB/95/M5/1	Processed oil only. Notification (1/6/97) under Novel Food regulation 258/97	Unpublished study: degradation of novel DNA and protein in stomach fluids of pigs, chickens, cattle.
Aventis' T25 maize	Approved under EU Directive 90/220/EEC Ref: C/F/95/12/07	Processed products (eg flour) only. Notification (12/1/98) under Novel Food regulation 258/97	Unpublished study examining the in vitro breakdown of novel PAT protein extracted from GM oilseed rape in digestive juices of cattle, pigs. Unpublished 14-day toxicity test of novel PAT protein (from GM oilseed rape) using rats. Unpublished study produced for Aventis - 42-day nutritional feeding study of T25 grain using broiler chickens.
Monsanto insect-resistant (Bt) maize MON 810	Approved under EU Directive 90/220/EEC Ref: C/F/95/12/02	Processed products (eg flour) only Notification (10/12/97) under Novel Food regulation 258/97	Results of an unpublished study produced by Monsanto in 1994 examining the in vitro breakdown of novel CryIA(b) protein in gastric juice and intestinal juice. CryIA(b) found in study to be rapidly degraded in gastric juices, but resisted breakdown (up to 19.5 hours) in intestinal juices. EPA MRID no 43439201. Results of an unpublished study undertaken by Monsanto in 1992: acute oral toxicity study of novel protein CryIA(b) protein in mice EPA MRID no. 43468001.

GM crop	EU approval for use in animal feed	EU approval for use in human food	Safety tests used to support applications for approval
Novartis/ Northrup King insect resistant (“Bt 11”) & glufosinate tolerant maize	Approved under EU Directive 90/220/EEC Ref: C/GB/96/M4/1	Notification under Novel Food regulation: 30/1/98	<p>Unpublished study produced by Monsanto in 1994 examining the in vitro breakdown of novel CryIA(b) protein in gastric juice and intestinal juice. CryIA(b) found in study to be rapidly degraded in gastric juices, but resisted breakdown (up to 19.5 hours) in intestinal juices. EPA MRID no 43439201.</p> <p>Results of an unpublished study undertaken by Monsanto in 1992: acute oral toxicity study of novel protein CryIA(b) protein in mice EPA MRID no. 43468001.</p> <p>In vitro examination of the breakdown of novel PAT protein in digestive juices of cattle, pigs and humans.</p> <p>Fourteen-day toxicity test of novel PAT protein using rats . Details unavailable - classed as information that is ‘commercial in confidence’.</p>
Aventis oilseed rape MS1/RF3	Not approved	Processed oil only. Notification under Novel Food regulation: 28/7/98	Notification based upon report by German Bundesamt für gesundheitlichen Verbraucherschutz und Veterinärmedizin. Details not available.
Monsanto glyphosate-tolerant oilseed rape GT 73	Not approved	Processed oil only. Notification under Novel Food regulation: 21/11/97	In vitro digestion studies of the novel GOX and CP4 EPSPS proteins.
Pioneer Hybrid insect-resistant maize MON 809	Not approved	Notification under Novel Food regulation: 14/10/98	<p>Degradation of novel proteins CP4 EPSPS and CryIA(b) in gastric fluids.</p> <p>Acute toxicity study (single large dose) in mice using novel protein CP4 EPSPS for 9 days.</p> <p>Acute toxicity study (single large dose) in mice using novel protein CryIA(b).</p>

GM crop	EU approval for use in animal feed	EU approval for use in human food	Safety tests used to support applications for approval
Aventis glufosinat e-tolerant oilseed rape derived from Falcon GS 40/90	Not approved	Processed oil only. Notification (21/11/97) under Novel Food regulation 258/97	Notification based upon report by German Bundesamt fur gesundheitlichen Verbraucherschutz und Veterinarmedizin. Details not available.
Aventis glufosinat e-tolerant oilseed rape derived from Liberator L62	Not approved	Processed oil only. Notification (21/10/99) under Novel Food regulation 258/97	Notification based upon report by German Bundesamt fur gesundheitlichen Verbraucherschutz und Veterinarmedizin. Details not available.
Plant Genetic Systems glufosinat e-tolerant oilseed rape MS8/RF3	Not approved	Processed oil only. Notification (21/10/99) under Novel Food regulation 258/97	Notification based upon report by German Bundesamt fur gesundheitlichen Verbraucherschutz und Veterinarmedizin. Details not available.

Alternatives

Inappropriate testing has been used as an assurance about the safety of GM foods for the last ten years. In May 2000, the OECD Task Force for the safety of Novel Foods and Feeds produced a report on the safety assessment of GM foods.⁹⁵ The Task Force was made up of officials from national governments around the world - 25 countries and the European Commission sent participants. The report of the task force says: “ Classical animal feeding trials are inadequate, due to the difficulty of feeding animals adequate doses of the test food in their diet. Increased research efforts and new techniques are needed to develop alternative safety assessment techniques for whole foods, especially in the areas of immunotoxicology, gut toxicology, molecular biology and plant physiology.”

If there is to be any kind of confidence in GM foods, better alternatives must be found. Increasingly, researchers are looking at in vitro tests using cells as a means of screening for effects. Tests exist which use liver cells or cells from the lining of the gut to assess the toxicity of chemicals, and some researchers have already suggested that such tests could be used for GM foods.⁹⁶ The use of cell-based tests for examining possible toxic effects is already common in the pharmaceutical industry for the initial screening of new drugs and the same approach could be used for GM foods. It is also important to examine what happens once the components in the GM food are absorbed into the body. So for example, various GM foods are in development which contain the snowdrop lectin. Researchers who examined the effect of this chemical on human white blood cells⁹⁷ found the chemical could bind to the blood cells, indicating a potential toxic affect. Research of this kind, which looks beyond simple animal feeding experiments, must be an essential part of the safety assessment procedure for GM foods. But isn't.

Without doubt, GM foods present a fresh challenge for food-safety testing and new techniques must be developed if their safety is to be assessed reliably. There is no easy way out or short cut for producers of GM foods, as far as consumers are concerned.

Allergic reactions

Genetic modification frequently makes use of proteins from organisms which have never previously been an integral part of the human food chain.

Allergic reactions are caused by an excessive immune reaction to particular substances (known as allergens) in susceptible people. Exposure to the allergen, such as by eating a food, inhaling pollen or by touch, triggers the production of an excess of immunoglobulin E (IgE) class antibodies. The development of an allergy may take time, but once it has developed there may be no safe level of exposure for the affected person. Allergies only affect a small proportion of the population, up to 2.5 per cent (although up to 25 per cent of the population self-report allergies), but the consequences can be severe, even deadly. In addition, the incidence of severe reactions appears to be rising, with the number of cases of anaphylactic shock increasing five-fold in the period 1985 to 1995.⁹⁸ The number of food substances implicated is on the increase, and there is also a reported increase in allergy to pollens.⁹⁹ There is concern that the introduction of novel proteins into GM foods could be a source of new allergies for sensitive members of the population and further increase this rising trend.

The approach taken by Monsanto scientists for the assessment of the allergenicity of novel proteins was published in 1996,¹⁰⁰ and similar approaches have been taken by other companies. If the novel protein originates from a plant or other organism known to cause allergies, then the allergenicity of the novel food can be assessed by using blood sera from people with an allergy to the source of the novel protein. This can be followed by tests on human volunteers if required. In a famous example, soya modified with a gene from the brazil nut, in order to increase the content of the amino acid methionine, was found to elicit an allergic reaction in people who were sensitive to brazil nuts.¹⁰¹ Because the source of the novel protein was known to cause allergies, it was relatively straightforward to test the GM soy, and its development was subsequently halted. But, as noted by the Monsanto scientists, if the

novel gene and protein comes from an organism that has never before been eaten as food, then it is of unknown allergenicity and the assessment is far more difficult. The scientists proposed that in this case, the novel protein should be compared to known allergenic compounds to see if there are any similarities. In fact, most of the novel proteins introduced into GM crops so far have come from sources of unknown allergenicity, such as bacteria or non-food plants, and this comparison approach has been widely used.

One of the assumptions often used in companies' assessments of the allergenicity of a novel protein is that allergens are usually found in large amounts in allergy-causing foods.¹⁰² But this is not always true - in the case of apples the main allergen makes up only 0.3 per cent to 1.5 per cent of total protein.¹⁰³ In fact, in the case of cow's milk allergy, it has been found that some allergic reactions appear to be caused by proteins that are only present in trace amounts, such as immunoglobulins or bovine serum albumin.¹⁰⁴ So, although many of the novel proteins found in novel foods are only present in small quantities, this is no guarantee of their safety.

Structural analysis

In the case of novel proteins from non-food sources, their amino acid sequence is established and this is compared to databanks of the amino acid sequences of known allergens. Around 200 allergens from food, pollens, mites and animals have been sequenced, and it is estimated that if eight amino acids are found in sequence in common with any of these allergens then there could be cause for concern. While this is an effective means of eliminating some potential allergens, it is limited by the fact that many allergens are not yet categorised. For example, beta-lactoglobulin, an allergen from cows milk, is not in the databanks and would not be identified using amino acid comparison either.¹⁰⁵ The fact that the amino acid sequence of a novel protein does not show any sequence similarities with the allergens listed in these databanks does not guarantee that it is not an allergen. In addition, it is not just the amino acid sequence but the shape of the protein (essentially how the chain of amino acids is folded) which determines its allergenicity. Many allergens of animal origin share a similar structure, but this cannot yet be used as a tool for identifying new allergens as the shape of only a very few allergens has been determined.

Digestion

Novel proteins are frequently examined for resistance to digestion. This is based on the assumption that the allergic reaction is caused by the whole protein and that allergens resist digestion. Experiments have shown that many food allergens resist digestion for up to one hour, while normal food proteins are broken down in less than one minute.¹⁰⁶ In most assessments, the novel protein is tested in vitro using extracted or synthetic gastric juices from a range of animals and humans. The rate at which the protein breaks down is seen as an indicator of its allergic potential. However, this experiment does not represent the real conditions under which novel proteins will be consumed. It does not account for the buffering effect of the other components of the food, which can help to delay digestion and lower the acidity of the stomach contents, again reducing the rate of digestion. Aventis has used in vitro digestion of the novel PAT protein to support its application for marketing approval for T25 and T14 GM maize. The experiment looked at the digestion of the PAT protein using gastric

juices from pigs, chickens and cattle at different levels of acidity (pH). However, when the report of this (unpublished) experiment was examined by Dr Vyvyan Howard, head of Fetal and Infant Toxicopathology at the University of Liverpool, he commented that the experiments used very acid gastric juices, and that such highly acid conditions would not occur if a real animal was eating the GM maize, because the GM food would itself reduce the acidity of the stomach contents. He concluded that: “The experiments do not represent a realistic assessment of the likely degradation of PAT protein in real animals.”¹⁰⁷

This type of test has a number of other failings. Some allergens, such as many of those found in fruit, elicit an allergic response in the mouth – before they enter the stomach. Resistance to digestion is an irrelevant consideration in these cases. Similarly, casein, an allergen from milk, would pass this test as it is rapidly broken down during digestion. There is also evidence that short segments of allergenic proteins can provoke an allergic response. Proteins may be ‘folded’ in such a way that short allergenic sequences are tucked away inside and so the whole protein does not provoke an immune response. During digestion, however, the overall structure can be broken down, potentially revealing these allergenic sequences. In fact, there is evidence that human IgE antibodies can react more strongly to broken-down proteins than the whole protein, with the possibility that the immune response occurs after digestion.¹⁰⁸

An in vitro digestion test cannot examine these subtleties and cannot establish whether an immune response will occur, only whether the protein has broken down. Once again, passing this test gives no guarantee that a protein will not cause an allergic reaction. The OECD’s inter-governmental Task Force on Novel Foods and Feeds has commented that: “Such testing may not always provide clear evidence of the possible toxic or allergenic potential of peptides formed as breakdown products in the test system. These problems suggest that there is a need to improve toxicity and allergenicity testing methods, especially for digestibility tests that simulate the gastrointestinal tract more precisely.”¹⁰⁹

In fact, the OECD Task Force recognised that there are no reliable methods for determining the likely allergenicity of a GM food before it is released. It was forced to fall back upon the use of post-release monitoring, stating that: “Until validated tests become available for reliable evaluation/prediction of a novel protein’s allergenicity, the record of reported allergenic reactions (which could be part of post-marketing surveillance) in relation to actual intake of the novel food would be a useful tool to guarantee complete safety for consumers.” It seems strange that, despite the many claims of industry, foods are being released into the food chain which will have to be monitored for adverse reactions in consumers. It should be remembered that monitoring does not guarantee safety to the consumer - only producing safe foods does that.

The GM smokescreen

Despite the large amount of testing of GM foods that has been claimed by biotech companies, very little of this has been peer reviewed or published. Dr Arpad Puztai was pilloried in 1999 for commenting on the results of a feeding trial using GM potatoes before the results had been published, yet this is exactly what the biotechnology companies are doing in support of their products.

- Novartis states in its public information: “Bt corn went through extensive safety trials in the laboratory, in the greenhouse and in the field. The results of these tests prove the safety of Bt corn for human or animal consumption or for use in cultivation.”¹¹⁰ Yet only one feeding trial using Novartis’ Bt176 corn has been published,¹¹¹ and Novartis has refused to make the detailed results of its other studies available to the public.
- With respect to maize containing Bt toxins, Monsanto comments: “Across the biotech industry, 19 animal-feeding studies using Bt corn have been completed or are in progress.”¹¹² Yet it appears that only one study (mentioned above) has been published.
- Aventis bases claims about the safety of its T25 and T14 maize varieties entirely upon unpublished studies, one of which was severely criticised by independent experts and considered not to be fit for publication.

How many of these unpublished reports, upon which the safety of GM crops rests, would be found adequate if subjected to an independent peer review? Why have only such a small number of these studies ever been published? Why are some not even available to the public? In a recent letter to the US journal *Science*, a Spanish researcher commented that after conducting a literature search on the Medline database, he found a large number of opinion pieces asserting the safety of GM food, but only eight studies which presented experimental data on this subject. He commented: “One of the more surprising results of this review was the absence of citations of studies performed by biotechnology companies. If, as I assume, safety and toxicity studies of GM foods have been carried out by these companies, why have the results not been subjected to the judgment of the international scientific community, as would be the course if such research were published in reputed journals?”¹¹³

Biotech companies cannot expect the public to have any trust in their products if they are not prepared to expose their safety testing to independent scrutiny. It is time to stop hiding behind unsubstantiated claims, and bring all the wealth of information they claim to have into the open.

5. *The US's GM guinea pigs*

While concerns about the safety of GM foods have emerged in most industrialised nations, and are increasing in developing countries as well, the US public remained remarkably unconcerned until late 2000. GM foods have been introduced very widely into the US food chain since the early 1990s, with minimal regulation or control compared with most other industrialised nations. This has been hailed by many as an example of progressive government and as a leap forward for the US consumer, but the real situation may be far less rosy. In fact, the contamination of the US food chain by the GM Starlink maize, which was only approved for use in animal feed, brought this issue to the top of the food agenda. It highlighted the fact that the development of GM crops and foods in the US has raced ahead of the country's ability to regulate them.

The US has the largest range of GM crops in commercial use of any country in the world. By the end of 2000 there were more than 45 different types of GM food approved for the market, including GM melon, maize (corn), tomato, potato, chicory, squash and papaya as well as foods derived from GM oilseed rape (canola), soybean, sugar beet, cotton, and flax. There is little information publicly available about how much of the US diet is made up of GM foods, but an indication is given by the fact that in 2000, 50 per cent of maize production in the US was GM, and 59 per cent of the soybean crop.¹¹⁴ The likelihood is that a majority of processed foods in the US now contains GM materials in varying proportions, but as there is no labelling requirement for GM foods, neither the consumers nor the authorities know how much.

In comparison with the EU, regulation of GM foods in the US is far more relaxed. In May 2000, the US Government finally declared that companies wanting to introduce GM foods would be required legally to consult with the FDA,¹¹⁵ but prior to this there was no statutory safety assessment of GM foods introduced onto the US market. Instead, there was a process of voluntary consultation with the FDA. In 1992, the FDA produced a policy document which stated that GM foods should undergo the same pre-market safety testing as food additives do under US law.¹¹⁶ However, US law states that only new food additives are required to go through thorough pre-market safety testing. If they are considered to have a long history of safe use, they can be classed as GRAS (generally recognised as safe), which removes the requirement for pre-market safety testing. The FDA's policy document went on to say, without any justification:

“In most cases, the substances expected to become components of food as the result of genetic modification of a plant will be the same or substantially similar to substances commonly found in food, such as proteins, fats and oils, and carbohydrates.”

With this statement, the FDA gave the green light to all GM foods - it is hard to conceive of a GM food which would contain an introduced compound that could not be classed as being a fat, protein, oil or carbohydrate. Since that date, the FDA has declared more than 40 GM foods to be GRAS, thus removing their obligation for pre-market safety testing.

The reasoning behind this was given in 1995 by an official of the FDA, who said: “ We believe that most of the substances that are being introduced into food by genetic modification have been safely consumed as food or are substantially similar to such substances.”¹¹⁷ But in fact, in the GM foods known to have been introduced into the US food chain between 1994 and 1999, there were 14 novel proteins from bacteria, seven from viruses and three from non-food plants. Only four novel proteins introduced into the US food chain are derived from existing food plants.

The complacency with which the FDA views GM foods has led to an astonishing attitude to their safety assessment. The FDA’s Centre for Food Safety and Applied Nutrition summed up the Agency’s approach:

“At Calgene’s request FDA evaluated the safety and nutritional data collected by the firm and issued its decision that the Flavr Savr tomato is as safe as other commercial varieties of tomato in May, 1994. **Following that decision, the FDA has not found it necessary to conduct comprehensive scientific reviews of foods derived from bioengineered plants based on the attributes of these products.**” (emphasis added)¹¹⁸.

In 2000, the US administration stated that the system of regulation for GM foods “has resulted in rigorous scientific review of products, while providing a predictable regulatory environment that fosters scientific advancement and product innovation” .¹¹⁹ However, where the balance lies between safety and product promotion is open to question. In fact, the FDA has approved more GM products for human consumption than any other regulatory authority in the world and this has, until recently, been based upon voluntary assessment. The EU has consistently taken a more precautionary approach to GM foods, and some indication of the greater rigour of their assessments is given by the following examples of responses of the UK authorities to applications received for GM foods that had already been approved by the FDA.

GM food/crop	FDA approval	UK competent authority comments on applications received
Sulfonylurea tolerant flax (University of Saskatchewan)	1998	“The transformation system was very dated and had an inherent weakness absent from more modern vector system [which] unnecessarily adds to the complexity of the risk assessment and the potential for pleiotropic effects.” “Members were further concerned about the block of three ARMs [Antibiotic Resistance Markers], two of which would be able to function in bacteria.” ACRE, 2000 ¹²⁰ Recommendation that product be rejected.

GM food/crop	FDA approval	UK competent authority comments on applications received
Glyphosate-tolerant maize (Monsanto)	1998	<p>“A lack of rigour in the original analysis of maize line GA21 and poor interpretation of the data had contributed to a standard well below that required and expected.”</p> <p>“The Committee considered that the applicant’s conclusion on the likelihood of expression of the truncated maize EPSPS was not fully justified from the data and advised that the applicant reconsider or submit more convincing evidence.” ACRE, 1999¹²¹</p> <p>Further information requested from applicant</p>
Male sterile chicory - radicchio rosso (Bejo Zaden BV)	1997	<p>Information received by the ACNFP “does not adequately address its concerns about harmful, unintended secondary effects from the genetic modification on phenotype and composition”.¹²² ACNFP, 1998</p> <p>Objection to marketing approval sent to European Commission</p>
Glyphosate-tolerant cottonseed (Monsanto)	1995	<p>“The Committee remarked on the general poor quality and number of inconsistencies in the submission.”¹²³ ACNFP, 1998</p> <p>“There was also concern regarding the apparent statistically significant differences seen in some of the components of the GM derived oils compared to controls e.g. in the levels of cyclopropenoid fatty acids.”¹²⁴ ACNFP 1999</p> <p>Further information requested from applicant</p>
Insect-resistant cottonseed (Monsanto)	1995	<p>“The Committee did not feel that the quality of the genetic data supplied was adequate.”¹²⁵ ACNFP, 1998</p> <p>Further information requested from applicant</p>

Without even a legal obligation on biotech companies to notify the FDA of GM foods going onto the market, until May 2000 the FDA was reliant on companies coming forward voluntarily. The weakness of this position was outlined by the FDA itself, when at an OECD meeting in 1998, it was minuted as stating: “The system does not require pre-market approval but companies are strongly advised to seek an assessment - so far about 40 products have been looked at and these are thought to be the only ones on the market.”¹²⁶ In other words, the FDA, which is charged with protecting the health of the US consumer, could not be sure how many GM foods were being sold to the US public.

The biggest feeding experiment in the world

“If you really want to start trials in humans, 300 million Americans have been eating GM soya for several years now without any ill effects.”¹²⁷

Professor Derek Burke, former head of the UK Advisory Committee on Novel Foods and Processes

There are more than 40 GM foods, containing at least 28 novel proteins, on sale in the US. The US Government has always resisted the concept of labelling GM foods, and this means that neither US consumers nor the various responsible authorities are able to tell what GM foods are eaten and in what quantities. GM foods like maize and soya are widely used in processed foods, meaning that routes of exposure to GM food products are diverse. Anything from fresh tomatoes to breakfast cereals, ready meals to soft drinks, could contain GM materials and the consumer is none the wiser. Recently, in response to public concern, some US companies have started to remove GM materials from their foods but the vast majority of food remains GM and unlabelled. For the last decade, the US public has been part of a huge, uncontrolled feeding trial of GM foods.

It is often said that there have been no adverse health effects of eating GM foods in the US. Leaving aside the possibility that the effects might not be apparent immediately, it is quite possible that health effects occurring now will not be picked up unless they are extremely dramatic. There has been no effort by the US authorities to look for health impacts. This is a simple case of “don’t look, don’t find”.

US consumers do not know whether they are eating GM foods - according to a poll in May 2000, only 43 per cent of American consumers were aware that GM products were sold at all.¹²⁸ So there is no reason why they should connect GM foods with any health impacts - ruling out self-reporting of GM-related illness. The only cases of self-reported illness linked to GM food have come in the wake of the Starlink contamination - in that case, the widespread publicity alerted people to exactly what foods contained a specific GM crop. This is not usually the case, and so not only is the US public part of a huge, uncontrolled feeding experiment, but the results are not being collected. Their value as guinea pigs has already been recognised in other parts of the world - the UK Government’s scientific advisors have noted that “in the US, GM foods have been consumed on a significant scale for four years and therefore Americans have had large exposure to this technology. Any recorded health data could therefore be invaluable”.¹²⁹

Even if the US Government did, at this late stage, attempt to monitor for health impacts of GM foods, it would be extremely difficult, if not impossible. To provide any meaningful results it would be necessary to establish population groups with varying levels of exposure and then to establish differences in health indicators due to the consumption of GM foods. With no labelling, and more than 40 GM products in the food chain, this would be a Herculean task. The exposure routes are enormously complex and exposure to a range of GM foods would be the norm rather than the exception. It would be necessary to establish

extremely detailed information about purchasing behaviour in order to determine the level of exposure individuals or groups receive. To isolate the effect of one out of 40 GM foods in the food chain would be almost impossible.

There is no indication that the US Government has even considered taking such action, but post-marketing monitoring of GM foods will soon be a requirement within the EU and, since 1998, the UK Government has been considering how such monitoring could be done. It has now been proposed that market survey data will be used to establish consumption patterns and that these will be correlated with systems already in place which routinely monitor health events, such as cancer, congenital anomalies, still births and birth weights. It is possible that a similar system could be applied in the US. Although the ACNFP has noted that relating consumption of GM food to health is a “notoriously difficult and complex” task, and that the potential for long time lags between exposure and health impacts adds to the complexity, at least it would provide some means of monitoring the impact of GM foods on the US population. In the end, the ACNFP concluded that the main value of such a system would be that it “could be rapidly interrogated if some potential health effect came to light, or if some cluster of health events were thought to reflect exposure to novel foods”.¹³⁰ Yet even this is not in place in the US - if health effects come to light, there is nowhere to turn.

6. Conclusions

The introduction of GM foods, additives and feeds has taken place in the absence of a safety assessment system that recognises that the techniques of genetic modification are still being developed with unpredictable outcomes. To continue with the current system in the present climate of public scepticism in Europe would be a mistake. Not only could a major public or animal health crisis result from inadequate screening before products enter the market, but public confidence in the process is also unlikely to be restored. A broad-reaching review of all possible procedures is required and positive involvement of consumers in the process will be required.

Enormous amounts of time and effort have been spent by governments and the biotech industry in presenting the image of GM crops and foods as being well regulated and as safe as non-GM foods. Yet there are specific hazards which arise from GM foods which are distinct from those arising from non-GM foods: there is the possibility, as a result of genetic modification, of significant alterations to the metabolism of GM food plants and there is the fact that most novel proteins inserted into GM crops are entirely novel in the food chain, and that these are being placed into a wide range of food crops. It is the major conclusion of this report that the safety assessment process, as it stands, is not adequate to pick out every GM crop harmful to human or animal health as and when it occurs.

Friends of the Earth believes the safety assessment of the of GM crops must be subjected to a full review in light of the following:

- GM crops are not the same as those produced by traditional selection breeding, particularly because of the random nature of genetic modification and the uncertainty of its consequences.
- The ability to detect differences in native genetic activity caused as a result of genetic modification, and understanding of their consequences, trails far behind the rate of development of GM crops.
- Difficulties in assessing the impacts of genetic modification will intensify as modifications become more complex.

Furthermore, Friends of the Earth believes the following procedures and practices are unacceptable:

- The presence of antibiotic resistance marker genes in a wide range of GM crops.
- The use of substantial equivalence as a tool for assessing the safety of GM crops and foods.

- The reliance on simple chemical analysis for examining the composition of GM crops and foods.
- The reliance on theoretical analyses for establishing the allergenicity of novel proteins.
- The use of inappropriate animal testing in support of the safety of GM crops and foods.
- The withholding from public scrutiny of detailed safety assessments by biotech companies.

Friends of the Earth believes the current systems of oversight cannot guarantee the safety of all GM products on the market. Gaps exist in regulatory procedures and their theoretical underpinnings, in the information provided in support of GM crops and in the ability to test the safety of GM foods. It is frequently argued that GM foods are no more dangerous than non-GM ones, and yet there is little scientific evidence to support this. While it is possible that many GM foods are as safe as their conventional counterparts, there is no system in place adequate to make this judgement, nor to detect any GM food that might be a real danger to consumers.

Food and feed safety is just one of many issues which need re-thinking by industry and the Government before they try to commercialise GM foods and crops. Important environmental, social, economic, cultural and ethical factors require as much consideration.

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