

ILSI EUROPE CONCISE MONOGRAPH SERIES



GENETIC MODIFICATION TECHNOLOGY AND FOOD

*CONSUMER HEALTH AND
SAFETY*

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ILSI EUROPE CONCISE MONOGRAPHS

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GENETIC MODIFICATION TECHNOLOGY AND FOOD

CONSUMER HEALTH AND SAFETY

by Clare Robinson



ILSI Europe

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FOREWORD

Consumers want, and expect, food to be safe and healthy. The supply, safety and nutritional value of foods have, over the centuries, been increased through innovation in plant breeding, crop harvesting and storage, and food processing and preservation methods.

Diverse approaches used to improve food quality and abundance have altered the genetics and physiology of organisms used for food production. Relatively few cultivated food crops bear much resemblance to their wild ancestors: tomato, for example, was developed from a toxic wild plant; and maize, like most cereals, from small-headed grasses of limited nutritional value. By selectively breeding plants and animals, or choosing the best strains of food bacteria and fungi, or deliberately introducing mutations that give desirable “improved” characteristics, the genetic make-up of such organisms has been radically altered.

The relatively recent use in food production of the techniques encompassed by the term “genetic modification” (GM) has attracted a great deal of attention. Undoubtedly, they allow the genetic make-up of organisms to be modified in ways not previously possible, but the aims of GM and “conventional” breeding techniques are the same. The more targeted approach of GM techniques avoids much of the hit-or-

miss of earlier methods, and provides novel opportunities to improve productivity, nutritional value and safety of food still further.

Nevertheless, increased awareness of the importance of diet on health, together with recognition that farming and food production has a major impact on the environment, has stimulated public concerns that the products of GM should be stringently assessed.

This monograph considers only the likely direct impacts of the consumption of GM-derived foods on consumer health and safety. Indirect effects on human health and safety – either beneficial or harmful – as part of the wider environmental impact are evaluated as part of the safety assessment required by legislation in various countries, but are not considered in detail here. Similarly, issues of consumer choice and labelling are referred to only briefly. At present, animals are being genetically modified for the purposes of basic and medical research, and for the production of human therapeutics: such animals are kept separate from the food chain. As yet, no animals are being genetically modified for food production, primarily because of ethical concerns and public perception. Hence, the potential future use of GM in food-animals is not covered in this monograph.

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CONTENTS

Biotechnology in the food chain	1
Technologies used to produce the food we eat today	1
How is genetic modification different from earlier technologies?	2
Is GM technology necessary?	4
GM-derived foods: the first generation	6
GM food crops	6
Genetically modified microorganisms (GMM) in food production	8
Food safety and gene technology	9
Sources of food hazards	9
Do GM-derived foods pose unique hazards?	14
What hazards might result from genetic changes?	14
Evaluating food safety	16
Substantial equivalence	16
How is substantial equivalence established?	16
From substantial equivalence to safety assessment	19
Safety of GMM in food production	24
Safety assessment of GMM	25
GM-derived foods: the second generation	26
Enhancing health	27
Enhancing health through food availability	30
Indirect consumer benefits	31
Gene technology in the future	32
Improved GM technology	32
The next step	34
Appendices	35
Appendix A	35
Regulation of the production and use of genetically modified organisms	35
Appendix B	39
Acronyms and glossary	39
Appendix C	42
Further reading	42
Appendix D	44
GM tomatoes	44
GM maize	44
GM soybeans	45

BIOTECHNOLOGY IN THE FOOD CHAIN

Genetic modification is just one of the most recent in the series of technologies applied over the millennia to food production. Advances in agricultural technology have aimed to provide a more abundant and consistent supply of food, and to increase the proportion of the crop available for human consumption by combating plant pests and disease. The importance of microorganisms in food production has long been recognised: although some microorganisms cause crop diseases and food spoilage, others have been used for food preservation, and to create new textures and flavours – indeed, entirely new foods, as through brewing, breadmaking and cheesemaking. These same natural fermentation processes of microorganisms are widely used to produce food additives, and enzymes for food processing. Together with the development of higher-yielding, more nutritious crop varieties, these advances have made the food supply more secure and affordable, and have increased the diversity of foodstuffs available. The use of biotechnology in food production is covered in detail in the ILSI Europe Concise Monograph: *Food Biotechnology – An Introduction*.

Technologies used to produce the food we eat today

Food crops

From the time that people changed from being semi-nomadic hunter-gatherers to a more settled farming lifestyle, food plants have been selected and nurtured for their characteristics of high yield, nutritional and flavour value, disease resistance and hardiness. Increasing understanding of plant biology has been paralleled by increasing sophistication in plant-breeding methods.

Traditional crop-breeding programmes have proved to be remarkably successful in combining and enhancing beneficial characteristics from related plants. For example, the yields of maize and wheat have doubled since the 1960s through plant breeding and altered agricultural practice. In the more recent past, it has not proved possible to continue increasing yield at such a rate, despite major efforts to address the problem: it appears that breeders may be encountering yield barriers that result from the plant's inherent genetic characteristics. This has led to a need for new approaches to be developed to enable food production to keep pace with the ever-increasing global human population growth. Because it is difficult to transfer genes for desirable characteristics between distantly related plants by crossbreeding, plant breeders have, over the past 40-50 years, used ingenious techniques to force some crosses that would not occur naturally, and to generate more variation than nature produces by:

- modifying the total number of copies of chromosomes;
- modifying the number of copies of individual chromosomes; and
- chemical and radiation mutagenesis to induce mutations and chromosome rearrangement.

Cell and tissue culture approaches such as embryo rescue, *in vitro* fertilisation, and protoplast fusion allow recovery of spontaneous mutants of a plant as well as producing hybrids between species and even between genera. Triticale, for example, is a man-made cereal crop resulting from combination of the genes of two different species, wheat and rye. Bombardment of a plant with chemicals or radiation causes mutations randomly throughout its genes, including mutations that plant breeders want, as well as mutations that are undesirable or have no value. By a lengthy process of crossing and

2 Concise Monograph Series

backcrossing, breeders can introduce and stabilize the new genetic characteristic into commercially valuable varieties (see Box 1). Characteristics for which mutant varieties have been selected include dwarfing, cold-, heat-, or salt-, and herbicide-tolerance, disease-resistance and crop male sterility (to facilitate hybrid production).

By the turn of the millennium, more than 1700 mutant varieties of 154 plant species had been officially released globally: among agricultural crops, cereals dominate with more than 820 mutant varieties (rice first with 318, followed by barley, wheat, maize and durum wheat). Unofficially, figures are likely to be even higher, and rising year on year.

Over the past half century, such techniques have revolutionised plant breeding, but their contribution to developing new crops is often overlooked.

BOX 1

Mutant malting barley

Golden Promise is a mutant barley developed by gamma-ray irradiation of another barley cultivar, and released in 1966. The short stem was associated with high yield and excellent malting quality: it was the main variety grown in Scotland throughout the 1970s and 1980s. Its mutated genes were transferred into another 17 released barley varieties.

Food-use microorganisms

Traditional food biotechnology makes extensive use of microorganisms (see Table 1). In many foods, microorganisms are essential to produce the food: yeasts produce alcohol in wine and beer, or carbon dioxide to make bread rise; and bacteria produce lactic acid in

fermented dairy, plant and meat products. In many such products, the microorganisms function during the production process, but are not present as viable (live) cells in the food product. In others, microorganisms will be present in the product: in “live” yoghurts, the presence of the organism is promoted as having beneficial effects.

Microorganisms are also widely used to produce supplements and additives (e.g. vitamins, amino acids, preservatives, citric acid, natural flavours and colours) or food-processing aids (e.g. enzymes). Enzymes purified from microorganisms are used to produce various hydrolysed protein derivatives, or ingredients such as high-fructose corn syrup. Many microorganisms used in food production have been modified by traditional mutagenesis techniques and selection similar to some of those used in plant breeding.

How is genetic modification different from earlier technologies?

Improving the characteristics of plant varieties or microorganisms for food use depends on creating, or making use of existing genetic variation. With traditional plant crossbreeding, there is no guarantee of obtaining any particular gene combination from the millions generated. Undesirable genes can be transferred along with desirable genes or, while one desirable gene is gained, another is lost, because the genes of both parents are mixed together and re-assorted more-or-less randomly in the offspring. Some genes – not necessarily with related functions – remain linked together, which can make it very difficult to separate some beneficial from detrimental characteristics by conventional breeding. These problems limit the improvements that plant breeders can achieve. In contrast, genetic modification techniques allow the direct transfer of one or just a few genes, between either closely or distantly

TABLE 1**Some common traditional food-use microorganisms**

MICROORGANISM	FOOD(S)
Bacteria	
<i>Leuconostoc spp.</i>	Dairy fermentations, sauerkraut
<i>Streptococcus thermophilus</i>	Cheeses, yoghurt
<i>Pediococci</i>	Vegetable fermentations (e.g. sauerkraut), fermented sausages (e.g. cervelat), oriental fermented protein foods
<i>Tetragenococcus</i>	Fermented fish; soy sauce
<i>Lactobacillus</i>	Dairy, vegetable, meat fermentations, breadmaking
<i>Propionibacterium</i>	Swiss cheeses
<i>Bacillus subtilis</i>	Oriental food fermentations (e.g. natto from soy)
<i>Bifidobacteria</i>	Dairy fermentations
<i>Brevibacteria</i>	Cheeses (e.g. Camembert, Limburger, Gruyere)
<i>Staphylococcus/ Micrococcus</i>	Meat fermentation (e.g. fermented sausages, cured ham)
<i>Enterococci</i>	Dairy fermentations, secondary flavour development in cheeses
<i>Penicillium spp.</i>	Food fermentations
<i>Halomonas spp.</i>	Cured ham
<i>Vibrio costicola</i>	Fermented herring
Fungi	
Yeasts	Wines, beers, bread, sake
<i>Aspergillus/moulds</i>	Mould-ripened cheeses, vegetable fermentations (e.g. tempeh)

4 Concise Monograph Series

related organisms (see Box 2). This increases the diversity of characteristics that can be changed, speeds up the process of improving the characteristics of food-use organisms (particularly plants), and makes it easier to track the genetic changes and their effects throughout assessment.

The techniques of chemical or radiation mutagenesis, used to generate a vast array of unknown genetic changes, are an integral part of “conventional” breeding. Providing the resulting plant or microorganism is still viable, and shows no identifiable toxicities, other mutations may remain unidentified. Mutant varieties are usually investigated only for the characteristics relevant to solving a particular breeding problem. For example, the rice mutant variety Atomita 2, released in 1983 for pest resistance and “earliness” (an important agronomic characteristic), was later found also to be salt tolerant. The same was found for Golden Promise barley. Such conventionally bred organisms are not viewed by the regulatory authorities as “genetically modified”^{*} and are therefore not subject to any additional GM-specific regulation.

Nevertheless, the approach of presuming the safety of new plant varieties from the known safe use of the parent lines, in conjunction with specific analysis of any components recognised as presenting possible nutritional and safety issues, has proved overall to be effective in ensuring food safety. Microorganisms used in traditional food production generally have a long history of safe use.

Is GM technology necessary?

The products of the first phase of commercialising GM crops have been perceived as benefiting primarily agribusinesses. Many people question the need to use GM technology in food production, with much of the debate inextricably linked with political aspects of globalisation of food production and trade. In industrialised countries, where a relatively small percentage of the population is directly associated with food production, the link between a healthy economy and individual consumer benefits is not obvious: in agriculture as in any other sector, market economies are driven by continuous innovation, and reduction of production costs. In addition, although most industrialised countries have surplus food, and the use of GM to enhance food production is sometimes seen as unnecessary, food reserves have a limited lifespan and are a dynamic resource that fluctuates considerably from year to year depending on harvest successes and failures.

An increasing global population with raised expectations is increasing the demand for food production: urbanisation and industrialisation are competing with agriculture for productive land. It is anticipated that, by 2020, China will need to import the equivalent of the 1999 total US cereal production. Africa currently imports 25% of its grain; its average maize yield is one-third – and sweet potato, less than half – the global average. Unpredictable and uncontrollable crop disease is another huge problem, particularly in developing countries.

The “Green Revolution” in cereal production in the 1960s and 1970s tripled the world food supply as the result of improved crop varieties (see Box 15), coupled with agrochemicals (fertilisers and pesticides) to

^{*} Definition of a genetically modified organism (GMO) according to EC Directive 90/219/EEC (1990) excludes mutagenesis and some cell-fusion techniques, and “self-cloning” of non-pathogenic microorganisms.

BOX 2

What is “gene technology” or “genetic modification”?

The breakthrough in understanding deoxyribonucleic acid (DNA) as the chemical double-helix code from which genes are made dates from 1953. In the 1970s, methods for making precise modifications to the genetic material of living organisms were first developed, and gene technology has developed rapidly over the past 30 years.

The term “genetic modification” (also sometimes called genetic engineering, or gene technology) is used to describe the process by which the genetic make-up of an organism can be altered using “recombinant DNA technology”. This involves using laboratory techniques to insert, alter, or cut out pieces of DNA that contain one or more genes. The ability to manipulate individual genes, and to transfer genes between species that would not readily interbreed, is what distinguishes genetic modification from conventional breeding techniques.

Genes and genetic modification

Genes are the instruction book for all inheritable characteristics, which usually means they direct the production of specific proteins. Genes are made of DNA (deoxyribonucleic acid) which is, in turn, made up of four different chemical building blocks called “nucleotides”. The individuality and function of a gene is determined by the number of these building blocks, and the particular order in which they are strung together – this is known as the “sequence” of the gene. The sequence of the gene, in turn, determines the identity of the protein that it encodes.

Genes from the same or other species (“transgenes”) that are to be used to genetically modify an organism have to be linked to other pieces of DNA sequences that control how they work. Genes (which encode proteins) need a sequence of DNA (a promoter) to switch them on (activation) so that they will start working (expression).

Because the process of genetic modification is relatively inefficient, with only a small proportion of the cells treated taking up and incorporating the transgene, “marker genes” are usually linked to the transgene of interest. Marker genes are easily detected by laboratory tests (e.g. the ability to survive a selection process such as treatment with a particular chemical – a herbicide or antibiotic, for instance). If the marker gene is present, it is likely that the transgene of interest is also present, thus enabling only those cells successfully modified to be saved for further development. Concern over the use of antibiotic-resistance genes as markers is leading to the development of alternative marker-gene systems, as well as of methods for removing marker genes.

Not all genetic modification technology involves inserting DNA from other organisms. Plants and microorganisms may be modified to remove or switch off particular genes. Genes can be switched off by inserting another copy, or partial copy, of a gene already present (a phenomenon known as “gene silencing”), or by inserting a reverse “antisense” copy of the gene. To illustrate the application, both techniques have been used to produce the delayed-softening tomatoes (see appendix D). Research is underway to use the same methods to switch off genes that encode allergenic (allergy-causing) proteins in some foods.

maximise yield. However, worldwide, nearly half of the crops grown each year are still lost to competition with weeds, diseases and pests – a figure comparable with farming in Europe 500 years ago. Globally, cereal crop productivity is actually falling, after a peak in the 1980s, as a result of various factors, including land-fertility exhaustion from multicropping, and loss of effectiveness of crop-protection chemicals. Further increases in yield with many existing crop varieties through conventional breeding seem unlikely. The use of GM technology is therefore extremely important in developing new approaches to increased food production, while reducing the environmental burden of agriculture and food production. Agricultural output can be increased by expanding the area of land under cultivation, or by intensifying production on land already under cultivation. The first is undesirable in terms of conserving land and natural resources – increasing productivity per unit area is the only practical solution to increased food production.

GM-DERIVED FOODS: THE FIRST GENERATION

GM food crops

The first transgenic plants were produced in 1984. Since then, more than 100 plant species, many of which are economically important crop species, have been genetically modified.

While a few crops have been modified for composition (altered dietary protein or oils, or industrial oils), most of the first generation of GM crops (i.e. those currently in, or close to commercialisation) aim to increase yields, and/or to facilitate crop management (see Table 2). This is achieved through the introduction of resistance to viral, fungal, bacterial diseases or insect pests, or through herbicide tolerance. Twenty to thirty percent of conventional crops worldwide are still lost to insects, and nematode pests destroy 100 billion Euros worth of crops annually, despite the use of chemical control. For some crops, especially in developing countries, the losses to post-harvest spoilage and insect damage are significantly higher, estimated to be as high as 80% for sweet potato in Africa. A major incentive for developing GM pest-resistant crops is to reduce widespread reliance on broad-spectrum insecticides and other pesticides. This would reduce production costs and environmental impact, as well as exposure of agricultural workers to agrochemicals and the levels of residues on foods.

GM insect-protected plants

Several different approaches are being used to develop GM insect-pest-protected plants. All those commercialised to date express genes derived from the common soil bacterium *Bacillus thuringiensis* (Bt) (see Box 3). Other insecticidal genes being used in developing GM

TABLE 2**First generation GM food crops**

CROP	BENEFIT*
Maize	Insect protection Herbicide tolerance Crop "male sterility"**
Oilseed Rape	Herbicide tolerance High lauric acid Crop "male-sterility"/"fertility restorer"
Papaya	Virus resistance
Potato	Insect protection Virus resistance
Soya	Herbicide tolerance High oleic acid
Squash	Virus resistance
Sugar Beet	Herbicide tolerance
Tomato	Delayed/improved ripening Reduced wastage Virus resistance
Chicory	Herbicide tolerance Crop "male sterility"

* The benefits of such first-generation crops accrue mainly to the suppliers and companies that own the intellectual property for the crops. It is a matter of debate to what extent the individual farmer and consumer benefits directly from any individual new product.

** Crop "male-sterility"/"fertility restorer" refer to characteristics bred into crops which prevent cross-pollination and the formation of less-valuable hybrids. They also act to protect the "intellectual property" of the plant breeder who developed high-value crops to minimise "escape" and wild crosses.

BOX 3**GM Bt insect-resistant crops**

Bacillus thuringiensis (Bt) produces crystals of the insecticidal protein (delta endotoxins) during sporulation: preparations of the spores or the crystalline protein have been used for nearly fifty years as spray insecticides, toxic to the target insects that ingest them when browsing on sprayed crops. Crop plants genetically modified to express the Bt toxin protect the crops by the same mechanism. The toxins are produced by Bt in an inactive form, which is activated by proteinases in the insect midgut: the toxin binds to receptors in the gut lining and damages it. Mammals do not possess these receptors and Bt toxins are therefore selectively toxic to insects and are not toxic to mammals. Different Bt toxins affect different insects: the specificity of the toxin depends on the conditions for activation in the gut, and the presence of appropriate receptors.

crops encode plant lectins, or inhibitors of digestive enzymes of pest organisms such as insect-specific proteinases and amylases, or they direct chemically mediated plant defence by plant secondary metabolites.

GM herbicide-tolerant plants

Herbicides are used to control weeds which reduce both crop yield and quality: weeds compete with crops for nutrients and light, and can also reduce the quality of the harvested product. For many conventional crops, fields are therefore usually sprayed with herbicide to control weeds before crops germinate. Thereafter, only selective herbicides which will not cause major damage to the crop can be used, but these do not kill all weeds. The use of herbicide-tolerant crops (see Box 4) can reduce overall herbicide use and the number of herbicides used because it is no longer necessary to kill the weeds before the crop seeds germinate. Herbicide-tolerant crops can be sprayed as necessary with a broad-spectrum herbicide if weeds become a problem; spraying at later stages can also be reduced because vigorously growing crops have a head start and weeds are less able to compete.

BOX 4

Herbicide-tolerant plants

Broad-spectrum herbicides such as glufosinate and glyphosate work by inhibiting amino acid synthesis in plants. Herbicide-tolerant GM plants have been obtained by inserting a gene, isolated from any of several soil microorganisms, into plants. Products from herbicide-tolerant GM maize, oilseed rape, soybean, and other important crops are on the market, although these crops are not yet grown commercially in the EU.

GM disease-resistant plants

Insects cause damage not only by eating plants, but also by spreading fungal, viral and bacterial diseases. All plants have natural defence mechanisms for protecting themselves against insects and diseases, but some are more resistant than others. Developing disease-resistant varieties of crops by traditional crossbreeding is limited by the ability to transfer resistance genes only between closely related species. GM technology allows disease-resistance genes to be transferred from other plants that will not interbreed with the crops, or from other organisms. Such GM crops expressing various plant or bacterial genes for proteins or enzymes that interfere with bacterial or fungal growth have been developed.

Where genes for effective resistance to particular diseases have not been found, GM allows another approach to be used, that of “immunisation”. GM virus-resistant crops have been developed using “pathogen-derived-resistance” in which plants expressing genes for particular viral proteins are “immunised” to resist subsequent infection (see Box 5).

BOX 5

“Immunising” rice against viral disease

Asian varieties of rice were introduced to Africa 600 years ago for their higher yield and better nutritional quality. However, they are more susceptible than native African varieties to diseases such as rice yellow mottle virus (RYMV), which can kill up to 100% of the young plants and renders older plants susceptible to secondary fungal infections. Traditional breeding methods have failed to produce high-yielding, RYMV resistant varieties because of species barriers. However, plants have an antiviral defence system that is conceptually similar (but mechanistically different) to the immune system of animals. It can be triggered, not only by intact viruses, but also by transgenes based on viral sequences. The possibility of creating novel viruses by transferring the transgene to naturally occurring viruses is unlikely because intact transgenes that encode functional protein are not required. The resistance trait can then be crossed into other valuable local varieties.

Genetically modified microorganisms (GMM) in food production

To date, no genetically modified microorganisms have been approved in the UK or elsewhere for use in food products – e.g. yoghurts, cheese – where they would be present as viable organisms. Yeast *Saccharomyces cerevisiae* strains are traditionally widely used in the production of bread, beers, wines and sake. Most such strains are inactivated by the food-production process and are not usually present as viable organisms in the end product. GM was used to improve the characteristics of both brewing and baking strains and such strains were approved in the UK in 1990, prior to current legislation. Despite the approval reflecting an absence of safety concerns, the strains were never introduced commercially because of consumer disquiet.

Although GMM are not themselves used in food products, many enzymes used in food production are now produced by GMM grown in large vats called fermenters. The GMM is separated from the enzyme product before the latter is used for food processing. In some cases, the product is more acceptable to specific consumer groups. For example, for some vegetarians, and those concerned with the potential risks from BSE (bovine spongiform encephalopathy), the use of GMM-derived enzymes in cheese production may be seen as a benefit. As well as the non-GM microbial rennet now available, a cloned calf enzyme has been produced. The gene for calf chymosin (an enzyme from the stomachs of slaughtered calves and used in cheese production) was inserted into food-use microorganisms, such as the fungus *Aspergillus*. It would also be impossible to provide an adequate supply of “traditional” calf chymosin: the global annual cheese production of 14 million tonnes requires 56000 kg of chymosin, equivalent to 70 million tonnes of calf stomachs.

With the exception of lysozyme in cheese, invertase in confectionary and glucose oxidase used as an antioxidant in soft drinks, most enzymes are used as processing aids, rather than as additives, in that they are inactive, degraded, or removed from the final product. Some 40 food enzymes are now also produced from GMM (see Table 3); this compares with more than 150 microbial enzymes overall used in food production.

FOOD SAFETY AND GENE TECHNOLOGY

Sources of food hazards

The word “food” is understood by most people to mean a substance that is eaten to provide nutrition, although the strict definition (see Glossary) covers any substance intended for human consumption. People also assume that food will not do harm, although it is recognized that many foods have to be prepared or stored in particular ways, and consumed as part of a balanced diet, for this to hold true. Indeed, most foods are derived from natural products, and therefore have associated natural hazards (see Box 6).

Potential hazards associated with food may derive from microorganisms, nutritional deficits and chemical substances which occur naturally in food (e.g. natural toxicants), which are introduced in the food chain

BOX 6

Risk versus hazard

The terms “risk” and “hazard” are often used interchangeably. However, “risk” = function of probability of an adverse effect consequent to a hazard (i.e. “risk” also takes into account the likelihood of the hazard). Hazards, whether biological, physical or chemical agents, cause an adverse effect when present at an unacceptable level. In the context of food, “hazard” refers to an intrinsic property (e.g. a food toxin) that has an adverse effect; risk takes into account the likely exposure and susceptibility of the consumer.

It is important to realize that no foods, including conventional foods, can be guaranteed to be absolutely safe, where “absolute” is interpreted as 100% safe under all conditions of growing, harvesting, storage and consumption for all sectors of the population. Approved foods constitute a “normal” risk, i.e. we know how to handle the residual risks and accept them.

TABLE 3**Commercial microbial food enzymes available from GMM***

ENZYME ACTIVITY	PRODUCTION ORGANISM	"DONOR" ORGANISM	FOOD APPLICATION
Alpha-acetolactate decarboxylase	<i>Bacillus amyloliquefaciens</i> or <i>subtilis</i>	<i>Bacillus</i> sp.	Beverages
Aminopeptidase	<i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp.	Cheese, dairy, flavours
Alpha-amylase	<i>Bacillus amyloliquefaciens</i> or <i>subtilis</i> <i>Bacillus licheniformis</i>	<i>Bacillus</i> sp. <i>Thermoactinomyces</i> sp. <i>Bacillus</i> sp.	Baking, beverages, starch Baking Beverages, starch and sugars
Arabinofuranosidase	<i>Aspergillus niger</i>	<i>Aspergillus</i> sp.	Beverages
Catalase	<i>Aspergillus niger</i>	<i>Aspergillus</i> sp.	Egg-based products
Chymosin	<i>Aspergillus niger</i> <i>Kluyveromyces lactis</i>	Calf stomach Calf stomach	Cheese Cheese
Cyclodextrin-glucosyl transferase	<i>Bacillus licheniformis</i>	<i>Thermoanaerobacter</i>	Starch
Beta-glucanase	<i>Bacillus amyloliquefaciens</i> or <i>subtilis</i> <i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Bacillus</i> sp. <i>Trichoderma</i> sp.	Beverages Starch
Glucoamylase	<i>Aspergillus niger</i>	<i>Aspergillus</i> sp.	Beverages, baking, starch, fruit-based products
Glucose isomerase	<i>Streptomyces lividans</i> <i>Streptomyces rubiginosus</i>	<i>Actinoplanes</i> sp. <i>Streptomyces</i> sp.	Starch Starch
Glucose oxidase	<i>Aspergillus niger</i>	<i>Aspergillus</i> sp.	Baking, egg-based products
Hemicellulase	<i>Bacillus amyloliquefaciens</i> or <i>subtilis</i>	<i>Bacillus</i> sp.	Baking, starch
Lipase, triacylglycerol	<i>Aspergillus oryzae</i>	<i>Candida</i> sp. <i>Rhizomucor</i> sp. <i>Thermomyces</i> sp.	Fats Cheese, fats, flavours Baking, fats
Maltogenic amylase	<i>Bacillus amyloliquefaciens</i> or <i>subtilis</i>	<i>Bacillus</i> sp.	Baking, starch

* from Association of Manufacturers of Fermentation Enzyme Products (AMFEP) data 13 April 2000

Pectin lyase	<i>Aspergillus niger</i> <i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp. <i>Aspergillus</i> sp.	Beverages, fruit-based products Beverages, fruit-based products
Pectinesterase	<i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp.	Beverages, fruit-based products
Phospholipase A	<i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp.	Baking, fats
Phospholipase B	<i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp.	Baking, starch
Polygalacturonase	<i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp.	Beverages, fruit-based products
Protease	<i>Aspergillus oryzae</i> <i>Bacillus amyloliquefaciens</i> or <i>subtilis</i> <i>Bacillus licheniformis</i>	<i>Rhizomucor</i> <i>Bacillus</i> sp. <i>Bacillus</i> sp.	Cheese Baking, beverages, cheese Fish-, meat-based products
Pullulanase	<i>Bacillus licheniformis</i> <i>Bacillus subtilis</i> <i>Klebsiella planticola</i>	<i>Bacillus</i> sp. <i>Bacillus</i> sp. <i>Klebsiella</i> sp.	Starch Beverages, starch Beverages, starch
Xylanase	<i>Aspergillus niger</i> <i>Aspergillus niger</i> <i>Aspergillus oryzae</i> <i>Bacillus amyloliquefaciens</i> or <i>subtilis</i> <i>Bacillus licheniformis</i> <i>Trichoderma reesei</i> or <i>longibrachiatum</i>	<i>Aspergillus</i> sp. <i>Aspergillus</i> sp. <i>Aspergillus</i> sp. <i>Thermomyces</i> sp. <i>Bacillus</i> sp. <i>Bacillus</i> sp. <i>Trichoderma</i> sp.	Baking, beverages Baking Starch Baking Baking, beverages, starch Starch Beverages, starch

deliberately (e.g. food additives, agro-chemical residues), or which enter adventitiously (e.g. environmental contaminants). For sectors of the population with particular sensitivities, food components such as food additives, considered safe and even desirable at routine concentrations, may also constitute a hazard. For example, sulphites, used as preservatives, can cause severe reactions in sulphite-sensitive asthmatics.

Microbiological safety of foods

Viable microorganisms from a variety of different sources are found in food: from the food material itself, from contamination from the environment, or by intentional addition for the valuable effects they have in

creating the food (e.g. bacteria and fungi in ripened cheeses). Many are harmless food contaminants, without either value or health risk (raw vegetables have bacterial counts of up to 30 million per gram). Others are toxigenic (produce toxins) or are pathogenic. Such bacteria and fungi constitute the greatest acute hazard to human health associated with food. Reduction or avoidance of exposure to pathogenic and toxigenic microorganisms is achieved by food processing and preservation to delay spoilage by microorganisms. Substances produced by the microorganism, as well as the microorganism itself if it is present in a viable state in the final product, need to be considered in assessing food safety.

Nutritional value

The variation in nutrient content is important because of the effects it has on the value foods have in meeting nutritional requirements. Human nutrition depends on a relatively limited number of crop plants, and the nutritional value is determined primarily by the content of carbohydrates, or fats, and proteins in either the seeds (for grain legumes and cereals) or in the vegetative storage tissues (e.g. potatoes and cassava), and of micronutrients (vitamins, minerals). Evaluating the impact of potential variation in nutrient content of a “novel food” (see Glossary) first requires an understanding of the role of a particular food in the diet. This, in turn, requires knowledge of the composition of diets across the full range of likely consumption levels. Potatoes for example, are a good source of vitamin C, and likely to be important in diets where citrus fruits feature rarely. In developing a new variety, a plant breeder should take this into account to ensure that levels of vitamin C are at least equivalent to those of traditional varieties that it may replace.

Inherent toxicants

Many plants contain toxins: some are self-defence substances to protect the plant against disease or stress, or against being browsed, while the function of others is unknown. Relatively few cause harm to people as part of a normal diet, although linamarin in lima beans and cassava root, lotaustralin in chick-pea, and solanine in potato are recognized as common toxicants (see Box 7). The level of toxicants in a particular food can vary widely depending on the environmental conditions while the plant was growing (for example, frost or drought can increase toxicants), care in handling or processing the plant material, and variety grown – the level of solanine can vary widely in different varieties of potatoes.

Such natural “toxicants” can, within limits, be tolerated if the foods are otherwise nutritionally valuable. Of course, the toxic effects of a particular substance depends on many factors: the amount of toxin in the food, the overall amount of food which is eaten and the extent to which the toxin is absorbed from the ingested food. The frequency with which the food is eaten can also have an effect: toxins which do not accumulate in body tissues pose less of a risk if they are consumed infrequently and the amount consumed at any one time is not harmful, whereas such a pattern of consumption has relatively less impact for toxins which can accumulate and build up to higher concentrations in the body.

In addition, inherent sensitivity to particular toxins varies from one individual to another. For example, people with a genetically determined sensitivity may have difficulty tolerating fava beans because of the vicine and convicine they contain. The likely levels of

BOX 7

Potato – a “conventional” food containing natural toxins

The cultivated potato is consumed daily by millions of people: potato consumption is exceeded only by that of wheat, maize and rice. Domestication of the potato reduced the level of natural bitter-tasting toxicants, the glycoalkaloids (GA) such as solanine and chaconine. If the potato were introduced today as a novel food, careful evaluation and extensive safety testing would be required to decide its suitability for human consumption, owing to the presence of these compounds. Because GA are present in a staple food that has been consumed for millennia, their effects have not been rigorously assessed as they would if they were synthetic additives. The levels of GA in commercially available varieties does not, in general, pose a risk, although factors such as cold weather, pest damage, bruising or other stress, or “greening” can result in toxicologically unacceptable high levels of GA.

intake as part of a complex diet, as well as inherent toxicity of a substance, are therefore considered in evaluating food safety. It is not only substances acknowledged as toxins that should be considered: several vitamins (e.g. fat-soluble A and D), trace minerals (e.g. iodine, copper, selenium) and other essential nutrients are safely consumed only within a relatively narrow range.

Antinutritional substances

Some plant proteins (e.g. lectins and protease inhibitors) have an antinutritional effect, i.e. they interfere with digestion and hence diminish the nutritional value of food. Unlike dietary proteins, most lectins are not digested. Several hundred lectins have been identified, many from important crop plants. Many exist in common foods, such as beans, and probably have no significant effect at the levels normally consumed. Some are toxic if the food is eaten raw, but processing – particularly heating – can reduce or eliminate the harmful effects. Cooking, which disrupts the integrity of less thermostable proteins such as protease inhibitors, can render many foods (e.g. kidney beans), but not all, safe.

Allergens

Over 160 different foods and food ingredients appear to be linked to allergic reactions, including most key grain, oilseed and vegetable crops, and components of very many processed foods (see Box 8). Dietary habits are a factor in determining the prevalence of particular allergies around the world. For example, peanut allergy is quite common in the USA, whereas atopic dermatitis in response to dietary rice is relatively frequent in Japan. Changes in existing patterns of allergies might be expected with “globalisation” of diets. Introduction of novel foodstuffs (e.g. such as the yellow-fleshed kiwi fruit recently introduced in the USA), and changes in dietary preferences (e.g. increased consumption of

peanut and peanut products in the USA and Western Europe, compared with elsewhere) can lead to altered patterns of food allergy. However, relatively few allergens have been identified as causing severe – sometimes life-threatening – food allergies. Allergens associated with egg, milk, fish, crustaceans, peanut, sesame, soybean, wheat and tree nuts are responsible for more than 90% of cases. The vast majority of food allergens are proteins, yet relatively few of the tens of thousands of different proteins in staple food-crops are allergenic. Most proteins are individually present in small amounts but some, such as the storage proteins of grains and nuts, can make up a substantial proportion of the total protein in a food.

BOX 8

What is food allergy?

Food allergy is the immune system’s adverse overreaction as a result of sensitivity to particular substances in an otherwise harmless food. True food allergies may involve several different types of immune response, but they are different from metabolic food intolerances (e.g. lactose intolerance), or food poisoning (e.g. toxins or histamines in fish). Approximately 1-2% of the adult human population suffer from food allergies. The commonest type of food allergy is the result of food proteins interacting with a specific type of antibody, immunoglobulin E (IgE). Sensitivity is a result of genetic susceptibility of individuals, coupled with their history of exposure to the substance.

At present, once an allergic reaction to a particular food has been identified, individuals with such sensitivity must eliminate that food from the diet. Some allergens in foods show cross-reactivity both with other food allergens, and environmental allergens, e.g. many vegetable food allergies are associated with an allergy to birch pollen.

Do GM-derived foods pose unique hazards?

Conventional methods of producing new varieties of crops and microorganisms are considered by some people to be inherently safer than GM technology. Foods from varieties developed through traditional breeding methods have been accepted for hundreds of years: new varieties, generated using the same methods, continue to be introduced. Varieties with essentially the same traits are being developed by GM technology through the transfer of one or a few genes. Yet the genetic and metabolic changes associated with traits such as disease- and pest-resistance, introduced by conventional techniques from wild species, are rarely characterised in detail. Subsequent analysis shows such resistance to be associated with proteins such as lectins, proteinase inhibitors, and other potentially toxic or antinutritional substances. It is quite possible to produce undesirable new combinations of genes by conventional breeding: potatoes with unsafe levels of toxic glycoalkaloids (see Box 7), and celery with high levels of psoralen irritants were bred this way. These examples illustrate the importance of rigorous evaluation, whatever the product or process used to make it.

The use of a particular method of breeding or GM does not therefore, by itself, give the resulting plant or microorganism a particular property – its properties will depend on what genes are transferred, and into what organism.

As it is the products which are consumed or used, it is the properties and safety of the products that must be considered, not the method of producing them. At present, across the EU, the products of GM are assessed more rigorously, on a product-by-product basis, than those of other methods of producing new varieties of food crops or food-use microorganisms. This is not because it is

believed that they pose greater risks, but it is a precautionary approach until greater experience is gained with the technology, and to address consumer concern. While the joint FAO/WHO Consultation on Food Safety (1996) recommended evaluation of GM foods based on “knowledge of the process by which the product was developed, and a detailed characterisation of the product itself”, it also concluded that “the use of these techniques does not result in a food which is inherently less safe than that produced by conventional ones”.

What hazards might result from genetic changes?

When the various mechanisms by which potentially hazardous substances may be introduced into foods are considered, GM-derived foods do not inherently pose unique risks. Nevertheless, GM-derived foods are scrutinised more closely under most regulatory systems around the world than are conventionally derived foods. Changes to the inherent nutritional characteristics, toxicity and allergenicity of foods might occur owing to changes in gene expression, whether these are brought about through traditional plant breeding techniques, or through GM.

The composition of foods might be altered by:

- inserted genes and their products;
- indirect or unintended effects of gene expression; and
- unintended mutations resulting from insertion of a gene.

Inserted genes and their products

The presence in foods of novel genetic material does not inherently constitute a novel hazard, as all genes are composed of the same DNA building blocks. Genetic

modification can alter the order of these building blocks, but leaves their chemical structure unaltered. We routinely eat gram quantities daily of intact genes from a wide variety of raw plants (e.g. salads), microorganisms (in “live” yoghurt, some cheeses, and unprocessed foods and drinks), and from animals (unprocessed or lightly processed eggs, fish and meat). GM does not increase the overall dietary intake of genetic material. Similarly, ribonucleic acid (RNA), which is produced in the process of decoding DNA to make proteins, is naturally present in all such foods. DNA and RNA not broken down by food processing are largely broken down on digestion and there is no indication that genetic modification alters their stability or digestibility. Because of the chemical identity of the DNA or RNA building blocks, there are no concerns about their toxicity. It is not, therefore, the inserted DNA *per se*, but the protein products encoded by the introduced genes, that need to be considered to determine potential hazards in terms of toxicity, allergenicity or altered nutritional value. It is therefore desirable to limit the insertion of DNA to that necessary to introduce the desired characteristic, and to avoid insertion of DNA of unknown function. GM allows the size of the piece(s) of DNA transferred to be limited to that required to confer a particular characteristic. This is in contrast to traditional breeding where large regions (frequently several orders of magnitude more than are transferred by GM) of uncharacterised DNA are routinely transferred across species and even genera.

Unintentional effects (“pleiotropy”)

Any technique used to direct a specific change in an organism’s genetic make-up may result in other, unintended, changes. Many introduced genes code for enzymes that catalyse biochemical reactions, with the intention of increasing a particular product of a reaction. By changing the flow-through in metabolic pathways,

this can also result in unexpected increases or decreases in other reaction products. This phenomenon, “pleiotropy”, is of concern where the safety or nutritional value of the food might be affected. The mechanisms by which biochemical pathways in plants and microorganisms are controlled are not completely understood, and immense variation occurs between conventional varieties, and even between breeding lines, of the same species. When a gene is transferred by GM, the biochemistry of its products is better understood than for most genes in traditional breeding programmes. As the one or more protein(s) produced from the inserted DNA are known, it is easier to characterise changes – even if it is not possible to detect all the changes with complete certainty – resulting from the introduction of a known DNA sequence.

Insertional mutagenesis

Random insertion of a gene can inactivate or change expression of genes already present, or could theoretically activate other, normally “silent”, genes. For example, the wild relatives of many crop plants contain substances that are toxic but whose amount has been reduced in the edible parts of the plant in the early stages of crop domestication, perhaps by switching off the genes encoding the toxins in those parts. As the mechanisms by which the genes are switched off are usually uncharacterised, there is concern that such genes could be reactivated either by conventional plant breeding or by applying GM techniques. The hazards posed by random gene insertion or rearrangement are thus the same for GM as for traditional breeding.

EVALUATING FOOD SAFETY

Most people take food safety for granted, but food is safe because our knowledge of the hazards and their control through appropriate preparation and processing enable rigorous hygiene and quality management standards to be imposed. If changes are made to the process by which a food is produced, the potential impact of the change on food safety and nutritional value must be assessed prior to marketing.

The factors that have to be considered in assessing the safety of GM-derived foods are thus the same as for any other food not previously safely consumed. Indeed, the EU Novel Foods Regulation introduced in 1997 (see Appendix A) is intended to address any novel foods, not just those derived by GM technology. Numerous international scientific organizations such as the FAO (Food and Agriculture Organization of the United Nations), and WHO (World Health Organization) have concluded that the potential hazards associated with GM technology are no different from those associated with techniques widely accepted as part of traditional breeding practices, provided the GM-derived product is thoroughly characterized in its molecular biology.

Substantial equivalence

Establishing whether a food derived from a genetically modified organism is safe to introduce into the food chain is based on comparing it with the most similar food which has a history of safe use. This common-sense approach, based on familiarity, is the concept of “substantial equivalence”. The concept has attracted criticism, in part owing to the misperception that substantial equivalence is the endpoint of a safety assessment, rather than the starting point. Establishing substantial equivalence, or the lack of it, is used to

determine what safety assessment needs to be carried out. This approach acknowledges that the goal of assessment cannot be to establish absolute safety: the important conclusion is that, if a food derived from GM is substantially equivalent, it is “as safe as” the corresponding conventional food item and should be treated as such. The concept has been developed through the contributions of several international independent organisations with expertise in this area and through specially convened groups of experts (see Box 9).

How is substantial equivalence established?

Establishing whether or not a novel food is substantially equivalent involves a detailed comparison (See Table 4) of the novel food with its “conventional counterpart”, the most similar existing food or food component. This involves identifying which important nutrients or possibly harmful substances (e.g. toxicants or anti-nutrients) may need to be screened for. This is, in turn, determined by knowledge of both the overall characteristics and genetic background of the organism, the source of the transferred gene(s), and the function of the gene(s) that have been modified. For example, in plants grown for protein or meal, the amino acid profile is an obvious requirement; likewise, for oil crops, the fatty acid profile is required. In oilseed rape, some glucosinolates are known toxicants: the minimum requirement is comparison of the four main alkyl-glucosinolates; whereas, in soybean, eight other toxicants/antinutritional factors should be measured.

Any processing the food undergoes, the importance of the food in the diet, the foods that the novel food is intended to replace, and the likely levels of consumption, must also be considered. For some products, food processing eliminates differences between a GM-derived food product and its counter-

BOX 9

The concept of “Substantial Equivalence”

Various organisations have made recommendations as to how the safety of GM-derived foods should be assessed.

- In 1990, a joint report by FAO/WHO established the concept that comparison of a novel product with a corresponding conventional one having an acceptable standard of safety is an important element of safety assessment.
- The Organization for Economic Cooperation and Development (OECD) extended this to develop the concept of “substantial equivalence”, and recommended it as the most practical approach to assess the safety of food products developed using GM techniques.
- The ILSI Europe Novel Food Task Force Report on the *Safety Assessment of Novel Foods* (1996) defined substantial equivalence as being: “for a single, biochemically defined food or ingredient – biochemical identity within the limits of natural diversity of the traditional counterpart of commerce; and for a complex food or ingredient, identity with a traditional food or ingredient as regards composition, nutritional value, metabolism, intended use and level of undesirable substances contained therein within the limits of known and measurable natural diversity of the traditional counterpart of commerce”.
- The Scientific Committee on Foods (SCF), an advisory committee to the EC, noted the distinction between the term “equivalence” (a legal term which applies to the inherent analytical characteristics of a food or food ingredient, and which may indicate the need for labelling with regard to origin and composition) and the concept of “substantial equivalence” as a comparative approach to safety assessment. Thus, the SCF agrees with the WHO, FAO and OECD in the interpretation of the meaning and significance of “substantial equivalence”. The SCF also noted that substantially equivalent foods may contain modified DNA, but otherwise be identical to their conventional counterparts.
- The Nordic Working Group on Food Toxicology and Risk Evaluation (NNT) suggested that, to determine substantial equivalence, multiple relevant parameters (e.g. natural toxicants, antinutritional factors, macro- and micro-nutrients, vitamins, allergens, etc., known to be associated with conventional varieties of the crop) should be considered, and that a minimum list of specific parameters be established for particular crops.
- The FAO/WHO consultation convened in May/June 2000 called for more extensive biochemical profiling of GM-derived foods of plant origin to enable any unintended changes in composition to be detected.

part, even if the GM crop and its conventional counterpart from which the products are derived might not be substantially equivalent. For example, a novel gene (say, for insect-protection) and its protein gene product could be present in a GM plant, but the derived highly purified oil would contain neither DNA nor protein. Furthermore, with analysis of the fatty-acid profile and other characteristic components which are present in the purified oil showing no differences, the GM-derived oil would be deemed substantially equivalent.

The key challenge in equivalence testing is the immense variability of foods and diets. Most foods, particularly those from plants, are complex mixtures of ingredients that vary widely in composition. Important differences in composition often occur between varieties of a particular crop plant, but variation also results from the conditions of growing, harvesting and storing the crop. Processing increases the chemical complexity of some foods (e.g. coffee) and decreases that of others (e.g. flour); heating almost invariably generates new substances. There is quite detailed knowledge of the major macronutrients and micronutrients in food,

TABLE 4

Factors for consideration in establishing substantial equivalence between a GM-derived food and its conventional counterpart*

(1) CHARACTERISATION OF GMO

Host/Parent organism

- taxonomic classification
- relationship with other organisms (notably, any relationship to known pathogens)
- history of food use
- known toxins, allergens
- key nutrients associated with derived foods
- known toxic or bioactive substances and anti-nutritional factors

Transgene and associated DNA

- identity and source of transgene and vector sequences (including promoter)
- transformation method
- function or mode of action of the protein(s) expressed from the inserted DNA

GMO

- phenotypic characteristics compared to host/parent organism
- characterisation of insert
- function, copy number, regulation, level and stability of expression of transgene(s), and expressed proteins

(2) CHARACTERISTICS FOR COMPARISON TO ESTABLISH SUBSTANTIAL EQUIVALENCE WITH PARENT/HOST OR CONVENTIONAL FOOD COUNTERPART

Plants

- morphology
- growth
- yield
- disease resistance, etc.

Microorganisms

- taxonomic characterisation
- physiology
- presence of plasmids
- antibiotic resistance
- infectivity
- host range
- ability to colonise gut (or other tissue)

Composition (for GMO or food product)

- key nutrients#
- key secondary metabolites, including toxicants‡
- key allergens

* Data derived from "Biotechnology and food safety" Report of Joint FAO/ WHO Consultations 1996 and 2000.

Nutrients: substances in a particular food deemed to play a role in the diet. Comprises major constituents (by volume), e.g. proteins, fats, carbohydrates; and minor constituents, e.g. vitamins, minerals

‡ Toxicants: toxicologically significant compounds inherently present in a species which, because of either their toxic potency or level, may be detrimental to health.

together with information on natural toxicants, and some essential oils and alkaloids, but relatively little is known of the many more minor, particularly non-nutrient, constituents of food. Knowledge of food composition, and its “normal” range, are essential to be able to assess whether compositional changes resulting from genetic modification are significant, and important, in changing either the safety or nutritional value of a food. When such evaluations of GM-derived foods are being carried out, the rather limited existing information on composition of conventional crop varieties can be improved by including appropriate conventional varieties for assessment in these studies. The profile of secondary plant metabolites, whether toxicants or not, is often characteristic of a particular species and provides a valuable “fingerprint” in establishing substantial equivalence. The EU has recently initiated a project to develop a database on crop composition with information on plant secondary metabolites, including toxicants, with corresponding data on biological activity profiles. The database, Biological Active Substance Information System (BASIS), is expected to be available in 2002.

From substantial equivalence to safety assessment

The comparative “substantial equivalence” approach leads to three categories for GM-derived foods, and this determines the safety assessment required:

- Category 1: the novel food is substantially equivalent to foods already available. Products substantially equivalent to an existing counterpart are considered to be “as safe as” the counterpart, and need no further safety assessment. Such foods are considered as safe as the traditional counterpart.
- Category 2: the novel food is substantially equivalent to a traditional counterpart, except for the well-

defined differences: the safety assessment focuses on these differences.

- Category 3: the novel food cannot be demonstrated to be substantially equivalent, either because the differences cannot be defined, or because there is no appropriate counterpart with which to compare it. Further evaluation of the nutritional and safety status of the food is required.

The majority of foods derived from GMOs will belong in categories 1 or 2. In the future, it is likely that some GM crops and derived foods will not be substantially equivalent – for instance, where there is intentional enhancement of the nutritional value of the food product (e.g. added vitamins) through GM (see Box 14). According to the data acquired as part of the equivalence testing, the requirements for testing the safety (toxins, antinutrients, allergens), nutritional value, and dietary significance of incorporating the food item into the diet, can be defined and assessed. If it is felt that the information available is insufficient for a thorough assessment, toxicological screening, including animal feeding studies, may be used. This is particularly the case where the food is likely to be eaten as a significant part of the diet, where a gene not previously consumed has been introduced or where the modification may cause multiple changes to composition. Such studies have to be designed very carefully. Where a GM-derived food differs by the presence of one or a few genes and their products, it is sometimes possible to isolate and test them by conventional toxicology methods as is done with food additives. It is important to be sure that the isolated substances are the same as they would be in the whole food, and that there are no additional unexpected changes. If there are doubts, then the whole food has to be tested. Conventional toxicity tests are difficult to carry out with whole foods because feeding large amounts of one particular food item can lead to apparent

adverse effects through nutritional imbalance or through abnormally high consumption of other unrelated toxicants naturally present in the food. Deciding which tests are appropriate takes very careful consideration of many factors.

Toxicants

Knowledge of the natural toxicants and the normal range of their levels in a food provides a benchmark for evaluating novel foods. During the development of novel varieties, whether by GM or conventional breeding, toxicants characteristic of a species are considered. For example, the levels of lotaustralin in chick-peas, and solanine in potato varieties, that can be safely consumed are used as reference points when assessing the new variety. This helps to ensure that exposure to such toxicants is within accepted experience.

Preceding the development of modern analytical methods, plant breeders have traditionally developed “rule of thumb” methods that were broadly effective. Because application of such methods persists, variation in the analytical rigour occurs – in Germany, for example, the experimentally determined glycoalkaloid content of potatoes is not a mandatory part of the data to be submitted for registration of a new variety. Breeders address this issue by assessing the bitterness of new potato varieties in the course of quality assessments.

Nutritional balance

Changes in food composition may be intentional with the aim of improving processing or nutritional qualities (e.g. altered starch composition in potatoes, altered levels of fatty acids in oilseed crops, altered levels of beneficial antioxidants in fruit and vegetables). Evaluation of the impact on overall nutrition is carefully considered (see Box 10), particularly if the product is intended to replace a conventional food item that is a

major dietary component. Evaluating the nutritional value of a food also has to take into account whether digestion releases the nutrients so that the consumer benefits. If either the nutrient is in a form that cannot be digested, or substances are present that interfere with the digestion of food items, nutrition can be impaired.

Allergens

Preventing problems with foods containing allergens relies on avoiding the transfer of known allergens into the food supply, and assessing all proteins encoded by introduced genes, regardless of source, for their potential as allergens.

Most proteins introduced in GM plants to date are similar to proteins already in the food supply and, in

BOX 10

When is nutritional evaluation needed?

STARCHES

Starch is a carbohydrate made up of two component polymers, amylose and amylopectin. Modification of starches to change the amount, structure, or relative proportions of these polymers, aims to produce starches tailored for specific purposes (e.g. improved gelling or thickening agents, or reduced oil absorption in fried potatoes). Only a significant change in the proportion of indigestible carbohydrate would justify a nutritional evaluation of the food product. Indeed, increasing the proportion of some indigestible carbohydrates (e.g. fibre) could have benefits in improving gut function.

OILS

Changes in the composition or structure of fats or oils (e.g. changes in the saturation of unsaturated fatty acids) could change the nutritional value or digestibility of a product. Evaluation for safety would be required if fatty acids not normally present in dietary oils, or fatty acids with known toxicity (e.g. erucic acid) were present.

BOX 11

Assessing protein characteristics for potential allergenicity

- Size of protein (most known allergens are large, 10-40 kilodaltons)
- Stability to digestion (most allergens are resistant to degradation by gastric acid and digestive proteases)
- Similarity of protein structure to known allergens
- Prevalence in food (allergenic proteins are typically present at relatively high levels in problem foods)
- Stability to food processing/cooking (proteins that are degraded by processing are of less concern in cooked or processed foods)

general, much is known about them. Considering whether or not a protein is likely to be an allergen takes into account many factors (see Box 11). Comparison with proteins already safely consumed would help to indicate that the introduced protein is unlikely to be allergenic.

Assessing potential allergenicity of GM products involves a computer-based comparison of the protein's structure with that of known allergens, to look for similarities in the region of a protein that binds the antibodies responsible for the allergic responses. An identical match of at least eight amino acids (the building blocks of proteins) in a particular order indicates that the protein may be an allergen. Some proteins fold into different shapes, and allergens whose antibody binding region is divided onto loops not immediately next to each other might not be picked up by this comparison. However, digestion or cooking often causes such proteins to unfold, thereby destroying the antibody binding site and its potential as an allergen.

Assessing how stable a protein is to digestion or food processing is thus helpful: allergens tend to be resistant

to both. Various protocols, which use digestive enzymes such as pepsin, exist for assessing likely digestibility in an "average gut". Because food sources may contain protease inhibitors or substances that inhibit or promote digestion, complete degradation of the protein being tested, or its resistance to digestion by pepsin, cannot provide certainty in predicting the allergenicity of a protein. Similarly, it is difficult to model the digestive capacity of the very young, the elderly, and those who suffer from achlorhydria (unable to produce stomach acid). As well as choosing the most appropriate enzyme digestion protocol, the investigator takes these factors into account, considering them in combination with all the other criteria used to predict allergenicity.

Heat processed and purified vegetable oils contain little, if any, protein and are unlikely to elicit allergic reactions: individuals allergic to soybeans, peanuts and sunflowers can normally consume such derived oils without ill effect. Other purified products, such as starches that contain no protein – whether from conventional or from GM crops – would similarly pose no problem.

If a gene from a known source of allergens is transferred into a food plant, it has to be proved that the resulting food does not contain allergens. Some plants – peanut, soybean, mustard, hazelnut, almond, wheat, rice, celery and tomato – contain allergens that are resistant to processing or cooking. All foods derived from such GM plants must be thoroughly evaluated, whether or not the new protein resembles known allergens.

The assessment approach has proven to be highly effective, as demonstrated for the Brazil nut 2S storage protein, introduced into soybean to increase its nutritional value (see Box 12). This example is frequently erroneously cited to demonstrate the dangers of GM, but immunoassays identified the

BOX 12

GM soybean containing Brazil-nut protein

Soybean is limited in its value as a major animal feed ingredient because of its natural low levels of sulphur-containing amino acids. The Brazil nut 2S storage protein, which is high in such amino acids, was engineered into soybean to improve the nutritional value of soy meal: expression of the 2S protein was a significant fraction of the total transgenic soybean protein. However, the Brazil nut is known to cause severe allergic reaction (anaphylactic shock) in a small proportion of the human population, and thus assessment was required to determine whether an allergenic protein had been introduced into soy. Using solid-phase immunoassay, sera from eight of nine individuals with a documented sensitivity to Brazil nut gave a positive reaction, indicating that the transferred gene encoded a major allergen. As soybean derivatives are used as ingredients in processed foods, this product was deemed unsuitable for further development and the project was terminated.

protein's allergenicity long before the product could have reached supermarket shelves.

In general, a sequential decision-tree approach is used to assess proteins derived from allergenic sources. Each stage provides increasing certainty about the likely allergenicity of the protein (see Figure 1).

The process of assessing potential allergenicity of novel proteins is continually revised as the scientific understanding of allergenicity improves. The introduction of novel foods has stimulated careful consideration of exactly how much we do and don't know about allergens in food. For example, although highly allergenic proteins are often present in high levels in allergenic foods, some allergens can apparently sensitise susceptible individuals at less than milligram (and possibly less than microgram) levels. It has also

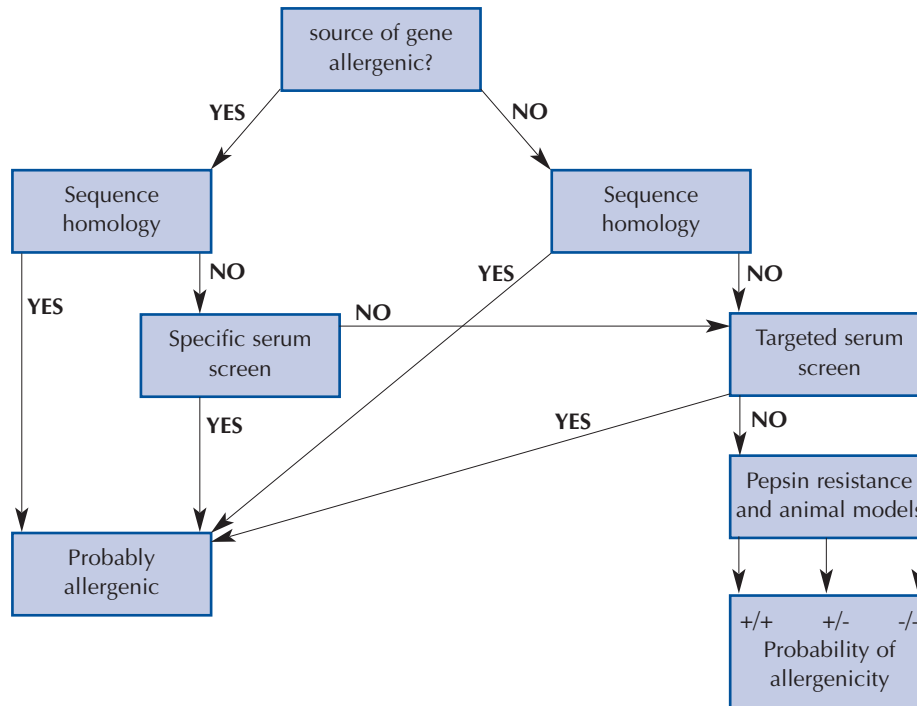
been recognised that it is not known whether the severity of the allergic response in individuals hypersensitive to less-commonly allergenic foods is any greater or less than for individuals to commonly allergenic foods. Recognition of this has led to revision of the FAO/WHO decision tree of 2000 to that of 2001 (see Figure 1) which no longer distinguishes between commonly and less-commonly allergenic foods. The final stage involves a "double-blind placebo-controlled food challenge" in which both sensitive and non-sensitive individuals consume the novel food and its "counterpart" under carefully controlled clinical conditions. If no reaction is observed, the GM-derived food is concluded to be non-allergenic.

Hazards from ingested DNA

As previously discussed, there are no unique toxicity or allergenicity hazards associated with the presence of genetic material in GMO-derived foods compared with conventional foods, as the chemical building blocks of DNA and RNA are the same. Ingested DNA fragments have been reported to be taken up into the cells of the gut, including the gut immune system, and into the circulation, of living animals. However, there are no reports of intact genes or even DNA fragments being incorporated into the genetic material, although humans and other mammals have always been exposed to foreign DNA in their food: digestive systems have probably evolved to prevent routine gene transfer from foods.

Concerns have been raised that gene(s) from GM-derived food materials could transfer to microorganisms in the gastrointestinal tract. There is no reason to believe that genes from GM plants are any more likely to be transferred than genes from any other plant: with regard to GM plants, "there is no recorded evidence for the transfer of genes from plants to microorganisms in the

FIGURE 1
Decision-tree for assessing potential allergenicity of GM-derived foods*



The initial stage of analysis focuses on the structural similarity of the protein (sequence homology) to known allergens. If it shows such similarity, it is assumed to be allergenic; if it does not, it is then tested for reaction with serum from individuals with known sensitivity to the source material (specific serum screen). If it does not react, it is then tested in the same way as proteins which are neither from an allergenic source, nor show any sequence homology – by looking for reaction in a “targeted serum screen”. This involves screening with serum from individuals allergic to materials related to the source material. For instance, if the gene is from a monocot plant, it would be tested against serum from patients allergic to grass or rice; if from a dicot, serum from patients allergic to various pollens, celery, nuts or latex would be used. Six classes of such organisms are distinguished: yeast/moulds, monocots, dicots, vertebrates, invertebrates and “others”. If no cross-reactive serum is found, the protein is then analysed for resistance to pepsin digestion and evidence of immunogenicity in various animal models. Where possible, animal testing is used to rank the potential allergenicity of the new protein against well-known strong and weak food allergens.

* The FAO/WHO 2001 Decision Tree, from Evaluation of Allergenicity of Genetically Modified Foods (2001). Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, 22-25 January 2001.

gut” (1993 WHO Workshop “Health aspects of marker genes in GM plants”). Such gene transfer is extremely unlikely because it would require:

- the DNA containing the intact gene to be released from the plant tissue and not be degraded by gastric acid or nucleases in the gut;
- the DNA to be able to cross the cell wall and cell membrane of a microorganism, and survive the microorganism’s machinery for degrading foreign DNA;
- the DNA to recombine into the host’s DNA and be stably integrated at a site where gene expression is possible; and
- the gene, if transferred, to be expressed in the microorganism. Genes modified to be expressed in plants are unlikely to be expressed in microorganisms.

Consideration of these factors and the GM techniques currently used led to the conclusion that “DNA from GMOs is as safe as any other DNA in food” (Jonas *et al.*, 2001, *Safety Considerations of DNA in Food*, *Ann. Nutr. Metab.*).

The likelihood of gene transfer from ingested DNA is therefore remote. Nevertheless, full molecular characterisation of the inserted genes is required as part of the evaluation process (see Table 4) together with consideration of the consequences of transfer, should it occur. To reduce any potential hazard still further, the use of therapeutically important antibiotic-resistance marker genes in GM plants is avoided, and additional genetic material not essential to the expression of the desirable trait minimised (see Box 13).

BOX 13

Antibiotics and antibiotic resistance

Antibiotics are chemicals, the majority of which are produced by microorganisms in the environment, that kill, or inhibit other microorganisms. Antibiotic resistance (the ability to be unaffected by the antibiotic) occurs naturally, and resistance to antibiotics is believed to have evolved hundreds of millions of years ago in soil bacteria.

There is concern that the use of antibiotic-resistance marker genes in GM plants might increase antibiotic resistance of microorganisms responsible for diseases in humans and animals, although any such problem is likely to be insignificant compared with the effects of widespread use of antibiotics in medicine and farming. However, the use of genes for resistance to non-medically important antibiotics is preferred. In addition, alternative types of marker genes are also being developed. In the future, it is likely that no new crops using antibiotic-resistance marker genes will be appearing on the market.

Safety of GMM in food production

The safety assessment of foods derived from genetically modified microorganisms follows the same principle of substantial equivalence as is applied to genetically modified plants. In addition, the safety evaluation of viable GMM for food has to consider issues not relevant to the safety assessment of foods containing non-viable GMM or derived from GM plants: the ability to colonise the human gut, cause disease or transfer genes to other gut bacteria. Although no GMM has yet been given approval for use as a viable organism in food, safety assessment procedures for their potential future use have been considered.

Colonisation

Assessment of viable GMM for use in food products must consider factors that would affect their survival and ability to colonise the gastrointestinal tract. Colonisation need not be harmful – many harmless and beneficial organisms colonise the gut. But microorganisms might, even if not in themselves harmful, have the potential to influence the vast numbers and diversity of the native gut flora and thus compromise gut function.

Pathogenicity

In general, microorganisms with a long history of safe food use are non-pathogenic (i.e. do not cause disease), and lack the genes encoding pathogenicity factors. Many GMM derived from such microorganisms will be similarly harmless provided no DNA carrying pathogenicity genes is introduced. Although rare, inactive or silent pathogenicity genes that might become activated, may be present. For example, strains of non-GM *Aspergillus* fungi that are widely used in food production possess the genes required to synthesise harmful toxins in a silent form. There is no reason to expect that GM would activate such genes but it is necessary to check for any unexpected consequences of DNA insertion.

Gene transfer

Microorganisms have well documented mechanisms for exchanging genetic material with other microorganisms. Viable microorganisms in food should therefore be selected to minimise their ability to exchange genetic material with resident gut microorganisms. In addition, they should not be derived from pathogenic microorganisms, or carry selectable marker genes that encode resistance to clinically important antibiotics.

Safety assessment of GMM

As in the case of GM-derived plants, a GMM will be assigned to one of three categories as a prelude to safety assessment. This permits comparison with the closest conventional counterpart microorganism already used in food production to establish substantial equivalence or otherwise and, thence, what evaluation is required (see Table 5). While the categories are broadly similar to those used to establish substantial equivalence for foods derived from GM plants, there is one major difference: to be in category 1 (i.e. substantially equivalent) the GMM should have no foreign genes added, and no changes in gene expression.

Where there is no directly comparable traditional food-use microorganism, or where those microorganisms traditionally used in food have not been fully evaluated – for example, for their potential to produce toxins or allergens – extensive testing would have to be carried out. Choosing a directly comparable organism can be difficult: many food microorganisms used in food fermentations show variation in characteristics upon continuous cultivation. Choosing an appropriate comparator would also have to take into account whether the microorganism remained viable in the final food product or not: although no such GMM have yet been used in food products, a more stringent evaluation would be required.

TABLE 5**Factors used in considering food-use safety of a GMM**

Host microorganism	<ul style="list-style-type: none"> • Taxonomy: what other species is the host related to? Are it and its relatives safe, or harmful? • History of use: does it have a record of safe food use similar to the use proposed? • Does it produce any harmful substances (e.g. toxins, allergens)
New genetic material	<ul style="list-style-type: none"> • If genetic material is inserted, is it from an organism with a history of safe food use? • Description of all the inserted genetic material, including key trait gene, marker gene, regulatory and non-coding sequences
Vector	<ul style="list-style-type: none"> • If any DNA which is not part of the intended insert is present, does it have a previous history of safe use?
GMM	<ul style="list-style-type: none"> • What is the DNA sequence of the actual insert, and the site at which it is inserted? Are there any deleted or inactivated genes? • Are the genetic changes stable? • Has the potential for gene transfer been increased? • Are the gene products as expected? • Are there any unintended effects; if so, do they constitute a hazard?

GM-DERIVED FOODS: THE SECOND GENERATION

Most “first generation” GM crops developed so far give improved agricultural performance, mainly by controlling insect pests or weeds more effectively, and result in higher yields. These will continue to be targets for additional and better “second generation products”, but other “second generation” products will focus on providing foods with enhanced or altered nutritional properties.

Such goals are nothing new: plant breeding to improve nutrition produced oilseed rape plants, known as canola, almost free of the toxic fatty acid erucic acid,

some thirty years ago. Canola oil now makes up a very large proportion of dietary lipids consumed in the developed world. The variety of foods consumed has changed greatly over the centuries, altering the nutritional composition of diets. The introduction of new foods and the increasing interest in foods which aim to provide health benefits beyond those merely associated with adequate nutrition will continue to change consumers’ diets. The availability of GM techniques, and the increasing knowledge of food function and human metabolism, will provide opportunities to develop such foods more quickly, and with greater precision. As yet, there are no foods from GM plants modified to improve their nutritional qualities commercially available, although there are some being developed.

TABLE 6**Characteristics under development/in field trials for “second-generation” GM crops**

<i>Crop</i>	<i>Characteristic</i>	<i>Crop</i>	<i>Characteristic</i>
Banana	Fungal disease resistance Ripening modification	Rice	Higher pro-vitamin A content Higher iron content Resistance to bacterial blight Resistance to rice borers Resistance to storage pests Fungal disease resistance Herbicide tolerance Increased photosynthetic capability
Cassava	Mosaic virus resistance Reduced cyanogenic glucosides	Soya	Insect protection Virus resistance Improved oil content Increased vitamin E Decreased levels of flatulent carbohydrates Improved flavour
Maize	Disease resistance Insect resistance Resistance to storage pests Higher starch content Altered starch structure High lysine, tryptophan content Improved protein content Increased levels of and modification of oil	Sugar Beet	Herbicide tolerance Altered macroingredient composition
Oilseed Rape	Improved disease resistance Improved oil composition Insect protection	Tomato	Insect resistance Virus resistance Disease resistance Improved quality/processing traits Increased lycopene
Oil Palm	Improved oil quality		
Potato	Insect resistance Fungal disease resistance Virus resistance Higher starch content Resistance to storage pests Bruise resistance		

Enhancing health

The influence of diet on health, by modulating the function of our immune, nervous, endocrine, circulatory and digestive systems, is increasingly apparent. Although genetic factors also play a role, differences in diet across different cultures are reflected in the prevalence of some disorders: in Japan, the shift from a

traditional Japanese diet to a Western-style diet has seen a drop in gastric cancer, but an increase in colorectal cancer. Increasing knowledge of the role of dietary factors in health and disease is enabling the design of physiologically “functional” foods that benefit health.

There are several categories of such products, in which GM technology might usefully play a role:

- removal or decreased levels of antinutritional factors, toxins, allergens;
- introduction or increased levels of health-promoting factors; and
- modification of the ratio of macro- or micronutrients (such as vitamins or minerals).

Removing detrimental substances

Dietary substances that cause health problems vary in importance around the world, depending on their concentration in the diet, the amounts consumed, and the sensitivity of the population.

Atopic dermatitis is caused by a globulin protein present in rice and is prevalent among Japanese children. The globulin is heat stable and resistant to proteolysis in the gut, and enzymatic destruction of the allergen to produce hypoallergenic rice is prohibitively expensive. Chemical mutagenesis of rice plants yielded a range of plants with reduced amounts of the allergen; however, those which produced only trace amounts were almost sterile. Significant reduction of the allergen by a GM antisense approach (see Glossary), or its removal by “knocking out” the gene entirely, without affecting agronomic characteristics, are already promising. Similar approaches could also work for allergenic proteins in peanut, soybean and Brazil nut.

Celiac disease is caused by the gliadin proteins in wheat, and is a debilitating gut condition for the approximately 0.015% of the population in Europe who suffer from it. Although not a classical allergic response, it should be possible to alleviate the problem by removing or altering the proteins responsible. Although there is much research on these proteins because of their

importance in determining baking quality, breeding wheat lacking the protein is not straightforward: whereas rice is genetically simple, wheat is a hybrid with multiple copies of genes from its ancestors.

Some lectins pose health and safety risks, and lectin-free or low-lectin crop varieties are being developed. For soybean and French beans, lectin-minus varieties have been found in plant breeders’ collections – commercial varieties can therefore be developed by classical selection and breeding. But some other crop species have multiple copies of lectin genes, making it unlikely that lectin-minus varieties will be found. GM techniques could be used to reduce lectins by inactivating lectin genes.

Cyanogenic glucosides naturally present in cassava cause a crippling wasting condition in people if the food is not properly prepared before consumption. Both acute and chronic toxicity are problems: low cyanogen varieties produce 20-40 mg hydrogen cyanide per kilogram fresh root; other varieties up to 20-fold more. Cassava is an important source of dietary carbohydrates, and is consumed by 500 million people worldwide. Traditional breeding is extremely time-consuming, and conventional crossing techniques do not work because of the way cassava reproduces. GM appears to be the only feasible approach at present to reducing the cyanogenic glucoside content of cassava.

Enhancing health-promoting substances

Some food components that are not essential nutrients nonetheless promote health. Consumption of higher levels of fruit and vegetables is associated consistently with a generally reduced cancer risk, especially for the gastrointestinal and respiratory tracts. Many different families of plant substances, often called “phytochemicals”, are probably involved in conferring such beneficial effects.

Some food factors play an important role by reducing the detrimental effects of free radicals – substances produced as a normal part of our metabolism, and increased by stress or various disease states. Plant flavonoids from fruit and vegetables are important dietary antioxidants, and phytoestrogens present in soybean may help to prevent cancers of hormone-influenced organs. Tea is rich in antioxidants with antimutagenic and anticarcinogenic properties. Organoselenium and organosulfur phytochemicals in allium species (e.g. onions, garlic) have a potential role in cancer prevention. However, it is important to remember that many bioactive phytochemicals have multiple functions, and beneficial substances may also be toxic at high levels of consumption. Simply increasing the concentration of specific phytochemicals in the diet may not yield health benefits. Indeed, a detailed assessment of safety and nutritional impact may be required if these components are consumed at levels in excess of those with a history of safe consumption.

Glucosinolates are a diverse group of plant substances with apparently equally diverse functions: playing a role in plant defence by acting as pest repellents; and acting as a protectant against stress damage. As part of the human diet, some glucosinolates are believed to have potent anti-cancer properties, yet others cause goitre. Brassica species are high in glucosinolates and the characteristic flavour and odour of different brassicas (e.g. bitter sprouts; mild broccoli) is owing to the particular glucosinolates present. Efforts are being made by both GM and conventional breeding to increase the level of glucosinolates which have both pleasant mild flavours and health benefits. Such work might help to promote increased consumption of health-promoting vegetables.

Vitamins and micronutrients

An estimated 800 million people survive on a limited diet of a few staples that do not provide adequate macronutrients. Micronutrient (vitamins, minerals and other non-essential, but health-promoting phytochemicals such as some flavonoids) deficiencies are even more common. Exhorting people to diversify their diet is pointless if the necessary crops are not grown locally and cheaply. Hence, efforts to enhance staple crops with some of the known beneficial phytochemicals are proceeding rapidly, exploiting GM techniques to target precisely the secondary metabolic pathways (see Box 14). Attempts to enhance levels of, for example, vitamin E, vitamin C and other

BOX 14

Golden Rice and vitamin A deficiency

Rice is a staple food in many highly populated parts of Africa, Asia and Latin America, but is deficient in several essential nutrients. Up to 124 million children have diets deficient in vitamin A and, in Southeast Asia, a quarter of a million children are irreversibly blinded each year as a result. Furthermore, vitamin A deficiency exacerbates diarrhoea, respiratory disease and childhood diseases such as measles. However, oral delivery of vitamin A poses problems, mainly because of the lack of a transport and distribution structure in some of the most badly affected regions. Ingo Potrykus of the Swiss Federal Institute of Technology, together with colleagues, developed GM rice supplemented with provitamin A (beta-carotene). No rice varieties exist which produce provitamin A in the endosperm (the nutritious grain) so a conventional breeding approach was not feasible. The entire beta-carotene biosynthetic pathway, with two genes originating from daffodil, and one from a bacterium, was introduced into rice. Because of the yellow colour of the grains, it has become known as “Golden Rice”. The developers of golden rice believe that it could help supplement vitamin A-deficient diets, by providing perhaps half of the daily vitamin A requirement in 300 g of rice per day, but full evaluation of the rice has still to be carried out.

micronutrients will require detailed knowledge of secondary metabolism, of optimal and upper safe micronutrient limits, and consideration of which crops to modify to achieve broadest benefit.

Altered fatty acid and starch composition

Oil composition of key oilseed crops are already significantly changed through plant breeding – canola oil (low-erucic acid rapeseed oil) has less than 5% erucic acid; and the “double-zero canola” has less than 0.1% erucic acid, compared with the approximately 50% found in its wild relatives. A GM canola containing a gene from California bay produced laurate-rich oil: this can replace tropical oils as ingredients in a variety of food products. The first laurate-rich canola was harvested in 1995. Other GM canola and soybean crops with altered oil composition (including increased oleic and stearic acids) are being developed for both industrial and food-processing purposes: oils with a healthier composition (e.g. containing unsaturated ω -3-fatty acids) can be developed. Many of these products no longer require chemical hydrogenation and hence will not contain trans-fatty acids, which have been linked to cardiovascular disease and possibly also some types of cancer.

GM crops with altered starch composition are being developed to tailor their usefulness for particular applications as thickeners, bulking agents and stabilizers in foods, as well as for other industrial non-food applications. Potatoes with altered starch composition that absorb less fat on deep-frying have been developed. “Designer” starches from GM plants also reduce the use of post-extraction chemical processing currently required to modify their structure according to use.

Enhancing health through food availability

For many people in the developing world, there is still undeniably a need to improve health by meeting basic calorie requirements through yield enhancement. So far, enhancing yield has focused on reducing loss to pests, weeds and diseases. There are, however, additional ways to increasing productivity, including:

- reducing susceptibility to adverse environmental conditions (heat, cold, drought, salt and other stresses);
- redirecting metabolism (shorter stems, more calories);
- improving carbon or nitrogen utilization; and
- altering plant development (to germinate or flower earlier; or to have a longer growing season).

Some crops are reaching the limit of maximum yield as imposed by their genes. Traditional breeding cannot increase yield much further, and breaking these “yield barriers” will often require modification of entire metabolic pathways to enhance or re-direct the plant’s resources into useful products. Sometimes the introduction of a single gene, such as a “dwarfing” gene, can have a major effect (see Box 15).

BOX 15

The dwarfing gene of the Green Revolution

Introduction of new dwarf varieties of wheats was the key factor in the increased agricultural productivity of the 1960s. The shorter stem means that plants are more resistant to damage by wind and rain, and more resources are directed into grain instead of stem (straw) production. The wheats are short because they fail to respond normally to the plant growth hormone gibberellin: the result of mutations at particular genes. Only in 1999, some thirty years after dwarf plants were introduced into agriculture were these genes identified. Height reduction in crops is frequently associated with increased yield, and introducing a single mutant “dwarfing” gene can now be used to reduce height in a range of crop species. Basmati rice is very tall and crop losses to wind damage are often high, but attempts by conventional breeding to reduce height had led to concomitant loss of its flavour and cooking characteristics. Introduction of the dwarfing gene reduced the height without affecting its other characteristics. The ability to introduce a single gene into any crop capable of being genetically modified, including varieties adapted to local growing conditions, should allow yield increases without disrupting other valuable traits.

Indirect consumer benefits

Reduced environmental burden

Many crop modifications whose primary goal is better agronomic efficiency have potential indirect consumer benefits through reduced environmental burden. The delayed ripening GM tomato, for example, which requires less processing because of increased solids-to-water ratio, indirectly benefits the consumer by reducing crop and energy wastage. Other traits being targeted that will reduce the environmental burden are crops that require less water, and use available nutrients more effectively. The potential for pest-resistant and herbicide-tolerant crops to reduce the overall agrochemicals use, promote conservation tillage, and allow use of less

environmentally damaging pesticides and herbicides, may be significant. For agricultural workers, there are also potential health benefits of reduced contact with or risk of inhalation of pesticides during application.

Reduced mycotoxins

While pest damage is probably not, in itself, detrimental to human health, the damaged plant tissues are even more prone to colonisation by bacteria and fungi. Many fungi produce mycotoxins, some of which are potent neurotoxins or carcinogens. More than 300 different mycotoxins are known, but only around 20 are viewed with concern in crops used for animal feed and human food. Stored peanuts are invaded by moulds (*Aspergillus* species) that produce aflatoxins, known carcinogens. GM maize, resistant to a major pest (European corn borer) showed significantly less insect damage, and consequent lowering of mould contamination and reduced mycotoxin levels, with up to 90% reduction in fumonisins. This type of damage is not only a problem in the field: insect pest and fungal infestation is a major health hazard post-harvest for stored products, and is currently controlled by application of pesticides and antifungal agents. Food safety with regard to mycotoxins is closely regulated.

Delayed ripening

Delayed ripening has the primary goal of reducing wastage as the softening of fruits and vegetables which is part of the ripening process leads to damage on handling. At present, many food crops are harvested under-ripe to avoid such losses during transport, but this also means that other aspects of ripening such as flavour development and sugar production do not occur. Delayed-ripening also minimises the loss of vitamins from foods prior to them reaching the consumer. Delayed ripening technology, initially developed for tomatoes (see Appendix D) has also been

applied in other crops: delayed-ripening strawberries, raspberries, cherries, melons and tomatoes, bananas, pineapples, peppers, papayas, cauliflower and broccoli are in development.

Better flavours

Flavour modification could have indirect health benefits by increasing fruit and vegetable consumption. Lipoxygenases, for example, are plant enzymes involved in plant defence, producing substances that kill pathogenic bacteria or stimulate healing. Some lipoxygenases also contribute pleasant flavours to fruit and vegetables, while others are responsible for “off-flavours”, that result from frozen storage of vegetables that have not been heat-blanching before freezing. Modifying the enzymes could improve both flavours and aromas. Through modification of enzyme pathways, it is also possible to retard or inhibit the browning of cut fruit such as apples, pears or bananas.

GENE TECHNOLOGY IN THE FUTURE

Increased crop productivity through enhanced metabolic efficiency, improved nutritional and other characteristics, and tolerance to disease and environmental stresses will help to meet increasing demands for food production. Many of the goals of GM are the same as those of conventional approaches, but GM can achieve them more quickly and in a less hit-or-miss manner. Information derived from gene technology, including knowledge from the worldwide “genome projects”, which aim to identify and understand the function and interactions of all the genes of a particular species, is increasingly valuable in conventional breeding approaches too. Information derived from the rice genome project will be widely applicable to other crops, particularly other cereals and grasses which all share common ancestors. Knowledge derived from gene technology will complement, rather than replace, conventional methods of developing novel genetic diversity. The use of molecular markers, for example, facilitates conventional plant crossbreeding and construction of novel GMM. With the development of techniques such as marker-assisted selection, the distinction between “conventional” and GM techniques is gradually blurring.

Improved GM technology

Experience gained with the first generation of GMOs has highlighted scientific questions that are being addressed in the research and development for second-generation products. These target improved predictability of GM, mainly through better control of transgene expression, and reduction in the use of unnecessary marker systems and other DNA sequences:

- removal of or improved marker systems;
- directed transgene integration: copy number, site of integration;
- transgene stability and inheritance;
- control of transgene expression (quantity, timing of expression, tissue specificity); and
- coordination of multiple transgene expression (metabolic engineering).

New marker systems

Concerns over antibiotic resistance marker genes are encouraging the development of alternative marker systems. Fluorescent proteins, such as the widely used Green Fluorescent Protein (GFP) of a jellyfish can be used as a visual marker, so that when a GFP gene is linked to the transgene of interest, the expressed genes can be detected by fluorescence of the protein under UV light. Methods for removing marker genes are also being developed.

Controlling where and when and how much transgenes are expressed

Most GM crops on the market use “constitutive” promoters that are permanently switched “on”. This means that the associated transgenes are active throughout the GMO’s lifetime. The use of constitutive promoters has been criticised, for example, as a possible factor in increasing the likelihood that resistant insect pests will evolve.

Although all cells of an organism contain the same full set of genes, not all genes are active all the time in all cells. Thus, although leaves contain the instructions for producing seed proteins, they are not active. Genes may also be switched on and off at appropriate times: some plant-defence genes, for example, are only switched on

during pest attack. Progress in identifying “switch control” is allowing expression of genes in GM plants to be targeted to particular parts of the plants such as roots or shoots, or only at particular stages of plant development. Thus, genes for pest resistance could be expressed in plant parts especially susceptible to a pest (e.g. roots are attacked by soil-dwelling nematodes), or at times to coincide with pest emergence (e.g. aphids in early summer). Activating genes only as necessary would reduce the drain on the plant’s resources and, in the case of pest control, reduces the likelihood of resistant pests.

Transgene expression levels and stability are still unpredictable because of differences in where, and how many, copies of the transgene insert. Integration of multiple copies of transgenes can trigger “gene-silencing”, whereby all the copies are inactivated. “Position-effect” silencing can occur as a result of transgenes integrating in “silent” DNA regions where genes are not expressed. Understanding how gene-silencing works is essential to develop effective ways of controlling transgene expression. Matrix-attachment regions (MARs) are DNA sequences which, particularly where flanking a transgene, appear to insulate the transgene from the effects of surrounding DNA, and can enhance both transgene expression and stability.

Metabolic engineering

Most GM crops to date are altered in the function of just a single key gene. However, many valuable traits now being targeted by GM will require the coordinated expression of multiple genes, in an attempt to engineer whole metabolic pathways. For example, insertion of a single gene could lead to production of a novel fatty acid at 20-40% total oil in GM oilseeds, but commercially valuable levels of 60-90% may require insertion of three or four transgenes. Plants have many mechanisms for controlling overexpression, and

enhancing the production of fatty acids (particularly unusual ones) in plants can stimulate lipid breakdown rather than accumulation. Integrating genes one by one is impractical and time-consuming, but techniques are under development to co-transform rice with ten or more genes simultaneously.

GM techniques do not yet permit control of either where, or how many copies, of the gene are inserted into the plant genome. But insertion may affect expression of neighbouring or more distant genes, either turning them off, or activating genes normally silent. Such changes could alter the composition of the plant, and establishing substantial equivalence requires this possibility to be considered. Techniques to do this are being developed:

- “differential display” to detect changes in mRNA levels for genes other than the transgene;
- “proteomics” to detect differences in the total pattern of proteins produced, including proteins with altered structures; and
- “metabolic profiling” to document amplification or suppression of whole metabolic pathways.

These tools will be extremely valuable but are still at an early stage of development. Much more research is required as well as validation before these methods could be used routinely for improved safety assessment or regulatory purposes.

The next step?

Although relatively few GM-derived whole foods and ingredients are as yet on the market, a large number of GM organisms with an increasing diversity of traits are under development and in trials. Extensive experience has already been gained on GM-derived foods. A wealth

of information about the composition of foods, including macro- and micro-nutrients, toxicants, antinutritional compounds and allergens, has been assembled not only for GMOs but also for conventionally derived foods. Thus, the knowledge gained should benefit consumers in enabling an improved safety evaluation of all novel foods, not just those derived through GM technology. In the case of GMO, the FAO has called for a cautious case-by-case approach to determine the benefits and risks of each GMO and to address the legitimate concerns for the biosafety of each product and process prior to release.

Understanding the genetic basis for plant and microbial physiology will aid both GM technology development and safety assessment. GM technology can also extend benefits achieved by conventional breeding. A good example of this is the dwarfing gene from wheat. Without gene technology, the genetic basis for the mutation and consequent benefits might have remained confined to use in wheat, as it has been for the past 30 years. With gene technology, the dwarfing gene and its cross-species relatives can be used to benefit productivity across any crop species capable of being genetically modified.

No individual technology or agricultural practice is, by itself, a solution to the challenge of ensuring food-supply security. Effective farming, harvesting, transportation and storage practices are all essential to improve productivity and food safety as well as to decrease crop losses. However, gene technology provides tools which, integrated into agricultural development strategies appropriate to local agroenvironmental and socio-economic systems, can help to meet the needs of a growing and increasingly urbanized population.

APPENDIX A

REGULATION OF THE PRODUCTION AND USE OF GENETICALLY MODIFIED ORGANISMS

In most countries where specific legislation has been introduced to control the production and use of GMOs, regulations distinguish between use in “contained” conditions (i.e. in the laboratory, or enclosed environment), and those where the genetically modified organism is “released to the environment” (i.e. for uncontained use in industry or in agriculture). Some countries rely on existing legislation in the areas of both environmental and consumer safety, while others have introduced legislation targeting products made using GM techniques. Regulations continue to be refined as experience demonstrates the safety of particular organisms or technologies.

European legislation

Environmental

Environmental legislation across the EU is based on two directives:

- Directive 90/219/EEC Contained Use of Genetically Modified Microorganisms (1990), amended as Directive 98/81/EEC in October 1998; and
- Directive 90/220/EEC Deliberate Release into the Environment of Genetically Modified Organisms (1990), currently under revision, with expected implementation by the end of 2002.

European legislation controlling the release of GMO requires risk to humans and animals as well as the environment to be assessed, so much of the information

(the potential for gene transfer, the safety of gene products and the question of substantial equivalence) is also relevant for food safety evaluation. Individual EU countries have the task of implementing these Directives through national legislation.

Food safety

In the EU, all countries have developed regulations to control food safety; most countries worldwide have some regulations imposed. For GM-derived foods, the requirements of Regulation EC 258/97 (the Novel Foods and Novel Food Ingredients Regulation) must also be satisfied. These harmonise procedures for the approval of all novel foods, including those produced by genetic modification, across Europe.

Novel and GM-derived foods

The European Regulation on Novel Foods and Novel Food Ingredients (EC258/97) came into force in May 1997 and requires a GM food to be labelled where there is a live GMO present, or where it might pose a hazard or ethical concern to a particular group of consumers. In addition, foods have to be labelled if they are “no longer equivalent” to existing foods or food ingredients, i.e. if they differ in characteristics or properties such as composition, nutritional value or intended use.

Specific GM maize and soya products were subject to labelling legislation subsequently introduced (EC 1139/98). Perhaps most importantly, EC 1139/98 provides a model for labelling similar approved novel products, whereby a novel [GM] food or ingredient is no longer considered to be equivalent to an existing [non-GM] one if protein or DNA from a GMO can be found. In October 1999, the EU Standing Committee for Foodstuffs recommended an amendment to this regulation: EC Regulation 49/2000 came into force in April 2000 and sets the *de minimis* threshold for adventitious GM-derived DNA or protein requiring

product labelling to 1% of individual ingredients. (Thus, a processed product containing maize starch as an ingredient would require the product to be labelled if the amount of GM maize starch as a proportion of all maize starch is 1% or greater.) As “adventitious” is taken to mean “unintended and unavoidable”, traces of GM-derived DNA or protein are only tolerable if, during preparation of both ingredient and foodstuff, all efforts could be shown to have been made to exclude GM-derived materials. Even if such care had been taken, if more than the *de minimis* level of GM-derived DNA or protein were present, it would not be regarded as adventitious.

Additives and processing aids

Additives were excluded from the labelling requirements of EC 258/97, but EC Regulation 50/2000, which came into force in April 2000, requires labelling of additives (as defined by Directive 89/107/EEC) and flavourings (Directive 88/388/EEC) derived from GMOs. Specification of additives and flavourings makes it apparent that processing aids are excluded, whether or not they are detectable. Legislation is currently based on indicating what is in the food: as enzymes are processing aids not considered to be present in the final product provided they are inactive and have no function in the final food, there is no requirement to label the product. Some companies have chosen to label to indicate the use of GM-derived processing aids, particularly where there is a perceived consumer benefit: GM-derived chymosin is more acceptable in cheese-making for many vegetarians. Adventitious contamination of additives and flavourings by GM-derived protein or DNA is recognised as a possibility, and EC 50/2000 leaves open the possibility of developing threshold values to trigger a labelling requirement.

Labelling and detection of GM-derived DNA or protein

The requirement for labelling products that contain GM-derived soya or maize “except when neither protein nor DNA from the genetic modification is present...” (EC Regulation 1139/98) has led to various methods being developed to detect the products of GM, as a means of enforcing the legislation. These include:

- Protein-based methods detect the transgene product. Degradation of food proteins during processing, limits the use of GM protein detection to raw foods.
- DNA-based methods detect either the transgene or associated marker or regulatory DNA sequences. Detection relies on a very specific and sensitive DNA amplification and detection technique called the polymerase chain reaction (PCR). Most GM crops and foodstuffs can be identified by PCR.

While raw foods can readily be identified as GM, detection is more difficult when they are processed: complex processed foodstuffs contain degraded DNA and substances that interfere even with the PCR reaction. Although PCR works on relatively short pieces of DNA, the more processed the food is, the harder it becomes to detect the transgene.

GM content or GM origin?

Highly purified oils or sugar from GM crops that were modified to contain genes for (for example) insect resistance, will contain no detectable protein or DNA – they are chemically identical to non-GM oil or sugar. They do not therefore need to be labelled.

Apart from the technical challenge, the wording of the regulation is problematic. The absolute absence of DNA or protein cannot be proved: however sensitive the analytical method used, it can only demonstrate the absence of detectable DNA. “GM-free” labelling cannot be supported by analysis.

The Novel Foods regulation and subsequent legislation now makes labelling mandatory for factors that reflect lifestyle (or ethical) issues, as well as for safety considerations, whereas other forms of “lifestyle” labelling (e.g. “organic”, “vegetarian”, “kosher”) are carried out by voluntary bodies.

This may complicate matters in terms of global harmonization of labelling legislation. Regulations on labelling vary around the world: in the USA, regulations do not currently require mandatory labelling and segregation of genetically modified crops and products.

US legislation

Three government agencies are responsible for regulating biotechnology in the United States:

- the United States Department of Agriculture (USDA);
- the Environmental Protection Agency (EPA); and
- the Food and Drug Administration (FDA).

Food safety

It is the FDA which is responsible for regulation of food safety, including food safety of new plant varieties, food additives and processing aids. In the Federal Register of May 29, 1992 (57 FR 22984), the FDA published its “Statement of Policy: Foods Derived from New Plant Varieties” which applies to foods developed from new plant varieties, including varieties that are developed using recombinant deoxyribonucleic acid (rDNA) technology (the FDA uses the term “bioengineered foods” for those derived by GM technology). The policy includes guidance on questions to be answered by developers of foods from new plant varieties, to ensure that the new products are safe and comply with

applicable legal requirements, and encourages the food industry to consult with the agency about the safety of new foods.

Labelling

The 1992 FDA policy also addresses the labelling of foods derived from new plant varieties, including plants developed by bioengineering. There are no special labelling requirements for bioengineered foods, as they are not considered to differ from other foods in any meaningful or uniform way or, as a class, to present any different or greater safety concern than foods developed by traditional plant breeding.

The labelling requirements that apply to foods in general therefore also apply to foods produced using biotechnology. A label must “reveal all material facts” about a food. Thus:

- If a bioengineered food is significantly different from its traditional counterpart such that the common or usual name no longer adequately describes the new food, the name must be changed to describe the difference.
- If an issue exists for the food or a constituent of the food regarding how the food is used or consequences of its use, a statement must be made on the label to describe the issue.
- If a bioengineered food has a significantly different nutritional property, its label must reflect the difference.
- If a new food includes an allergen that consumers would not expect to be present based on the name of the food, the presence of that allergen must be disclosed on the label.

Comparison of the US and the EU approaches to regulation

Considering the differences in approaches to regulation highlights some of the key issues under debate. In the US, foods derived through the use of GM technology are not considered to be, *a priori*, different from other foods developed through other technologies: they are therefore subject to the same food safety legislation as any other food. Under this legislation, the introduction of a gene from one food crop to another would not, by itself, trigger a need for evaluation and approval before the food is placed on the market, unless the gene encoded a product (e.g. a sweetening agent) that had never before been a component of any other food. If the food were modified in such a way, it would constitute a novel food and require regulatory approval. The sweetening agent itself would be regarded as an additive and therefore subject to other regulatory approval processes.

The key difference is in the approach to labelling. In the US, labelling is legally required to provide meaningful information to warn and instruct the consumer: further unnecessary information is believed to conflict with the right of the consumer to make informed choices, and to lessen the effectiveness of the labelling. If GMOs are not considered different from their traditional counterparts in terms of nutrition, composition or safety, GM labelling might be construed as misleading. In the EU, labelling is seen as assisting consumers to make an informed choice by indicating the use of GM or presence of GM-derived ingredients. The EU's approach to labelling attempts to address consumer demands, as well as meeting safety and nutritional requirements for accurate labelling of ingredients: the question is how to label, rather than whether to label. Nevertheless, the US introduced (17 January 2001) proposals for new guidelines and rules that would require food developers to notify the FDA of new biotechnology-

derived products 120 days before they are put on the market: the current system calls only for voluntary consultation for products that are substantially the same as their conventional counterparts. The proposals also provide direction to companies who wish to voluntarily label their food as made with, or without, ingredients derived through biotechnology.

APPENDIX B

Acronyms

DNA	deoxyribonucleic acid
FAO	Food and Agriculture Organization of the United Nations
GM	genetically modified/genetic modification
GMM	genetically modified microorganisms
GMO	genetically modified organisms
OECD	Organization for Economic Cooperation and Development
RNA	ribonucleic acid
SCF	Scientific Committee on Food (European Commission)
WHO	World Health Organization

Glossary

Allergy: Adverse overreaction of the body's self-defence system caused by the production of antibodies against specific substances.

Amino acids: Building blocks of proteins. About 20 different amino acids are commonly used by cells to make proteins.

Antibiotic: Compounds that inhibit the growth of, or kill, microorganisms. Many organisms (mostly bacteria and fungi) produce antibiotics of medical or veterinary value.

Antibiotic resistance: The ability of a microorganism to destroy or be unaffected by an antibiotic. Genes which encode antibiotic resistance are widespread in nature.

Antibodies: A class of proteins (known as immunoglobulins) formed in the body as a protective response to the presence of antigens (foreign proteins and other compounds).

***Bacillus thuringiensis* (B.t.):** A naturally occurring bacterium present in soil and used successfully by home gardeners and organic farmers for more than 30 years to control certain insects. When ingested by these insects, a protein produced by B.t. interferes with the insect's digestion, and acts as an insecticide.

Antisense technology: A GM technique whereby expression of a particular gene can be greatly reduced or eliminated by inserting a second copy of the gene in reverse orientation – this interferes with expression of the corresponding gene already present. This is one approach that has been used to produce delayed-ripening tomatoes (see Appendix D).

Biotechnology: The application of living organisms to the production, modification or processing of materials. By this definition, encompasses traditional plant and animal breeding, brewing, bread-making and effluent treatment, but more usually used to refer

to the use of techniques of genetic modification or fermentation technology in industry, agriculture, and environmental remediation.

Chromosome: In the cell, DNA is tightly packaged together with particular proteins into structures called chromosomes. Packaging into chromosomes enables the organized assortment of genes into daughter cells upon cell division, as well as playing a role in controlling gene expression.

Deoxyribonucleic acid (DNA): A long molecule made up of repeating units (each unit contains deoxyribose, a sugar, a phosphoric acid and a base) joined together in a particular order. Each DNA molecule consists of two strands in the shape of a double helix. Genes are made of DNA, and are responsible for the transfer of genetic information from one generation to the next.

Enzyme: A protein produced by living cells that regulates the speed of the chemical reactions that are involved in the metabolism of living organisms, without itself being altered in the process. Also called a "biological catalyst".

Fermentation: Conversion, catalysed by enzymes, of organic substances by organisms, especially bacteria, fungi or yeasts to produce other substances (e.g. conversion of sugar by yeasts to make wine) of biological origin. It may be intended, as in brewing of beer or vinegar, or unintended and undesirable, as in food spoilage. Also used to refer to the process of growing microorganisms or individual cells of plants or animals for the production of various chemical or pharmaceutical compounds. Large tanks, called fermenters, contain microorganisms or other cells and the nutrients they require to live and grow.

Food: The Codex Alimentarius Commission defines "Food" as "any substance, whether processed, semi-processed or raw, which is intended for human consumption and includes drink, chewing gum and

any substance which has been used in the manufacture, preparation or treatment of food, but does not include cosmetics or tobacco or substances only used as drugs".

Functional food: Foods can be regarded as functional if they have one or more targeted benefits, beyond providing adequate nutrition, such as an improved state of health or a reduced risk of a particular disease. They remain distinct from "medicines" in that they must remain as foods and be consumed as part of the diet.

Gene: The segment of DNA on a chromosome that contains the information necessary to make one protein. A gene is the unit of biological inheritance.

Genetic modification: The techniques for removing, modifying or adding genes to a living organism. Also called "gene splicing", "recombinant DNA (rDNA) technology" or "genetic engineering". "Within-species" genetic modification is essentially similar to traditional breeding methods (except that it is much speedier and much less haphazard). Through "trans-species" modification, results are obtainable that could not be obtained by traditional breeding methods.

GMP: "Good manufacturing practice" (GMP) is that part of a food production operation aimed at ensuring that products are consistently manufactured to a specified quality appropriate to their intended use.

Herbicide: Any chemical substance that is toxic to plants.

Mycotoxins: Toxic substances which can cause a variety of health problems, including cancer, and which are naturally produced by fungi. When fungi grow on plants, feeds and foods, dangerous levels of mycotoxins can accumulate.

Mutagen: A substance (e.g. chemical) or process (e.g. irradiation) that can cause damage to DNA.

Mutation: The change in the DNA sequence caused by damage by a mutagen, or by errors in cellular processes that may occur during cell division. Some mutations have no effect on the function of the genes in which they occur, while others inactivate or change the activity of the genes. Some mutations are detrimental to the organism, a few are beneficial. Mutations are a source of variation between individuals, and are a driving force of evolution.

Novel food: Food, or food ingredients produced from raw material, that has not hitherto been used (or has been used only to a small extent) for human consumption in the area of the world in question, or that is produced by a new or extensively modified process not previously used in food production. In the EU, the definition applies only to foods not used to a significant degree within the EU and which fall into one of the categories of the “Novel Foods Regulation”.

Pathogen: An organism that can cause disease in another organism.

Pesticide: A chemical used to control pests, such as insects, weeds or microorganisms.

Processing (food): Any and all processes to which food is subjected after harvesting to improve its appearance, texture, palatability, nutritional value, keeping properties, ease of preparation, and for eliminating microorganisms, toxins and other undesirable constituents.

Processing aid: Any substance not consumed as a food ingredient by itself; used intentionally to facilitate the processing of raw materials, foods or their ingredients. Residues of processing aids may remain in the final product provided they are non-functional and don't present a health risk.

Protein: Polymers (chains of linked units) of amino acids. The uniqueness of individual proteins depends

on their length and order of amino acids within the proteins.

Yeasts: Fungi, which usually grow and reproduce by budding. The brewing and baking industries rely on the ability of yeasts to produce enzymes that convert sugar into alcohol and carbon dioxide, respectively.

APPENDIX C

Further reading

Publications:

Astwood, J.D., Fuchs, R.L. (1996). Preventing food allergy: emerging technologies. *Trends Food Sci. Technol.* **7**, 219-226.

Conner, A.J., Jacobs, J.M.E. (1999). Genetic engineering of crops as potential source of genetic hazard in the human diet. *Mutation Research* **443**, 223-234.

Coulton, F., Kolbye, A.C., Eds. (1990). Biotechnologies and Food: Assuring the Safety of Foods Produced by Genetic Modification. *Reg. Tox. Pharmacol.* **12**;3;2.

Della Penna, D. (1999). Nutritional genomics: manipulating plant micronutrients to improve human health. *Science* **285**, 375-379.

Diplock, A.T., Aggett, P.G., Ashwell, M., Borner, F., Fern, E.B., Roberfroid, M.B. (1999). Scientific Concepts of Functional Foods in Europe: Consensus Document. *Brit. J. Nutr.* **81**, Suppl.1.

Franck-Oberaspach, S.L., Keller, B. (1997). Consequences of classical and biotechnological resistance breeding for food toxicology and allergenicity. *Plant Breeding* **116**, 1-17.

Jonas, D. (2000). Safety Assessment of Viable Genetically Modified Organisms Used in Food. *ILSI Europe Report Series*. ILSI Press.

Metcalfe, D.D., Fuchs, R.L., Townsend, R., Sampson, H.A., Taylor, S.L., Fordham, J.R. (1996). Allergenicity of Foods Produced by Genetic Modification, in CRC Press Assessment of the Allergenic Potential Derived from Genetically Engineered Crop Plants. *Crit. Rev. Food Sci. & Nutri.* **36**, S165-S186.

Ohlrogge, J. (1999). Plant metabolic engineering: are we ready for phase two? *Curr. Op. Plant Biol.* **2**, 121-122

Zechendorf, B. (1999). Sustainable development: how can biotechnology contribute? *Trends Biotechnol.* **17**, 219-225.

Reports and Guidelines

** Recommended as providing comprehensive introductions to core key topics of monograph.

**ANZFA (Australia New Zealand Food Authority). (2000). GM Foods and the Consumer: ANZFA's Safety Assessment Process for Genetically Modified Foods. Canberra, Australia/Wellington, New Zealand. Available from <http://www.anzfa.gov.au>.

FAO/WHO (1991). Strategies for assessing the safety of foods produced by biotechnology. Report of a Joint FAO/WHO Consultation. World Health Organization, Geneva., Switzerland.

FAO/WHO (1996). Biotechnology and Food Safety. Report of a Joint FAO/WHO Consultation, 30 September–4 October 1996. *FAO Food and Nutrition Paper*, **61**. Rome, Italy.

**FAO/WHO (2000). Safety aspects of genetically modified foods of plant origin. Report of a Joint FAO/WHO Expert Consultation of Foods Derived from Biotechnology, 29 May–2 June 2000. WHO. Geneva, Switzerland.

**FAO/WHO (2001). Evaluation of Allergenicity of Genetically Modified Foods. Report of a Joint FAO/WHO Expert Consultation on Allergenicity of Foods Derived from Biotechnology, 22–25 January 2001. FAO/WHO. Rome, Italy.

IFPRI (International Food Policy Research Institute) (1999). World Food Prospects: Critical issues for the early twenty-first century. *IFPRI food policy report*. 29. Available from:

<http://www.ifpri.cgiar.org/pubs/fpr/fpr29.pdf>

ILSI Europe (2000). Safety Assessment of Viable Genetically Modified Micro-organisms Used in Food. Consensus Guidelines. *Microb. Ecol. Health Disease*. 1;4:198-207.

ISAAA (International Service for the Acquisition of Agri-Biotech Applications): Food safety evaluation for the products of biotechnology (1995) (The ISAAA Food Safety Initiative) Available from:

<http://www.isaaa.org/publications.htm>

**Jonas, D.A., Elmadfa, I., Engel, K.-H., Heller, K.J., Kozianowski, G., König, A., Müller, D., Narbonne, J.F., Wackernagel, W., Kleiner, J. (2001). Safety Considerations of DNA in Food. *Ann. Nutr. Metab.*

Nuffield Foundation: Genetically modified crops: the ethical and social issues (2000). The Nuffield Foundation, London, UK. Available from:

<http://www.nuffieldfoundation.org/bioethics/publication/modifiedcrops/>

OECD (Organisation for Economic Cooperation and Development). (1993). Safety evaluation of foods produced by modern biotechnology: concepts and principles. OECD, Paris, France.

Shahidi, F. Ed. (1997). Antinutrients and phytochemicals in food. *ACS Symposium Series*. 662. ACS (American Chemical Society), Washington, D.C.

Websites

<http://vm.cfsan.fda.gov/>
(US FDA/Center for Food Safety and Applied Nutrition [CFSAN]: a major source of information on many aspects of food safety, consumer advice, and regulatory information.)

**<http://www.agbiotechnet.com/>

<http://www.fda.gov/oc/biotech/>
(US Food and Drug Administration's pages on food biotechnology)

<http://www.foodbiotech.org/>
(The Food Biotechnology Communications Network [FBCN] Canadian focus; broad information on food biotechnology)

<http://www.hc-sc.gc.ca/english/food.htm#novel>
(Health Canada's pages on novel and genetically modified foods)

<http://www.nal.usda.gov/fnic/>
(The Food and Nutrition Information Center [FNIC]: part of the U.S. Department of Agriculture [USDA] and the Agricultural Research Service [ARS])

**<http://www.ncbe.reading.ac.uk/NCBE/GMFOOD/>
(National Centre for Biotechnology Education [NCBE] is part of the University of Reading, UK. Basic information on GM technology, substantial equivalence, regulation.)

<http://www.oecd.org/subject/biotech/>
(Organization for Economic Cooperation and Development: pages on biotechnology news, views and publications)

<http://www.who.int/fsf/GMfood/index.htm>
(World Health Organization's pages dedicated to GM-derived food)

APPENDIX D

Genetically modified tomatoes

The first GM whole-food product to go on sale (in the USA in 1994) was a GM tomato, the FLAVR SAVR™ tomato produced by the US company Calgene Inc. The first product to arrive in UK supermarkets, in 1996, was a tomato purée manufactured from genetically modified tomatoes and produced by Zeneca Plant Science.

Tomato ripening

Tomatoes are usually picked while they are still under-ripe (i.e. green), and then treated with ethylene (a natural ripening gas) to turn them red. This keeps them firm during transportation and storage. Tomatoes turn soft, and ultimately rot, when an enzyme (polygalacturonase or pectinase) that is naturally found in the fruit breaks down the cell walls.

Genetic modification slows ripening

In the above GM tomato products, the polygalacturonase enzyme production was reduced by two different mechanisms: in the FlavrSavr tomato, the gene for polygalacturonase was copied and reinserted backwards (GM “antisense” technology); in the Zeneca tomato, part of the polygalacturonase gene was copied and inserted. In both cases, this “switches off” the polygalacturonase, pectin levels remain high, and the tomatoes soften more slowly. The GM tomatoes can remain longer on the vine to develop their full flavour (and colour), but stay firm enough to be transported to the market.

Less waste and improved processing

The major advantage of these modified processing tomatoes is less wastage: because of the higher solids to water ratio, less energy is used in processing and the addition of thickening agents in food processing is reduced.

Genetically modified maize

Two characteristics that are important to maize growers (agronomic traits) were introduced into maize using genetic modification. These are protection against the European corn borer, and tolerance to the herbicides glufosinate or glyphosate. The European corn borer causes extensive crop loss, and is currently controlled by application of chemical pesticides.

Maize products in food and feed

Processed grain products from GM maize do not differ significantly from those of the conventional crop. In the processed maize, none of the introduced genes is present in an intact form. For this reason, the processed maize products were deemed safe for use in food and animal feed.

Safety concerns over unprocessed genetically modified maize

There has been concern over the use of the “marker” antibiotic-resistance gene in the development of the GM maize. Although the antibiotic-resistance gene is not functional in the maize, the UK Advisory Committee on Novel Foods and Processes (ACNFP) said that, even though the risk was very small, the gene might be transferred from non-processed maize to bacteria that naturally live in the gut of farm animals. The concern was that this might allow gut bacteria to become resistant to the antibiotic ampicillin, and that this could lead to increased antibiotic resistance in either farm animals or humans. However, the European Union Scientific Committees on Pesticides, Animal Feeding-stuffs and Food decided that the risks of transfer were so low as to be unlikely to cause increased antibiotic resistance in either farm animals or humans. The European Union Council of Ministers therefore gave marketing consent for the first GM insect-protected genetically modified maize in January 1997.

Genetically modified soybean

Food products containing GM glyphosate-tolerant Roundup-Ready™ soybeans arrived on European supermarket shelves in 1997. Roundup-Ready™ is a broad-spectrum (i.e. kills many species of plants) and biodegradable herbicide, which is not highly toxic to animals and humans. The producer company claims that correct use of the GM soybeans and the herbicide is both environmentally beneficial and agriculturally cost-cutting: by eliminating the need to use herbicides to kill weeds before the soybean crop starts to grow could reduce herbicide use by one-third.

Environmental safety

Assessments of the environmental safety of the soybean, under the European Union Deliberate Release Directive (90/220/EC), resulted in approval for soybeans to be marketed in the European Union for the purposes of food processing, but not for cultivation. However, GM soybean has been approved for cultivation in the USA, Argentina and elsewhere and has increased each year as the proportion of the total soybean crop.

Food safety

Both US and European regulatory authorities decided that the GM soybeans are equivalent to other soybeans in terms of food safety and nutritional value.

Commodity versus specialty crop production

Soybean is a commodity crop, which has implications for food processing and consumer choice. Individual farmers usually grow 4-6 soybean varieties and pool the different varieties together. Over 1000 herbicide-tolerant varieties are now on the market. Food processors also pool soybeans from many locations. This keeps the prices down but makes tracing the source of soybeans impractical. Soybeans are converted into a wide variety

of industrial, food and feed products, including flour, oils and lecithin. Segregating GM and conventional soybean crops is feasible but costly, and market size for non-GM will probably dictate whether costs are passed on to the consumer.

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