

GENETICALLY MODIFIED FOOD

Executive Summary

1. The aim of this paper is to initiate the formulation of the Board's policy on genetically modified (GM) foods, taking into account the Government's current position and the existing regulatory controls. The paper does not address the cultivation of GM crops, except where they impinge directly on food safety matters.
2. The paper explains the current procedures for the safety assessment and labelling of GM foods and places these in the context of the European pre-market approval system. It also describes how the two Strategic Commissions on biotechnology, established by the Government last year, link in with the work of the Agency. A number of international initiatives related to GM foods are also discussed.
3. The Board is **invited to decide** whether it is content with the existing safety controls and assessment procedures but to await the outcome of existing consultations on food and feed labelling before deciding its position on GM labelling.

Additives and Novel Foods Division

Contacts: Mr Nick Tomlinson Tel: 020 7238 6377 (GTN 238 6377)
Dr Jon Bell Tel: 020 7238 5574 (GTN 238 5574)

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Issue

1. To invite the Board to begin the process of determining its policy on genetically modified (GM) foods, taking into account the Government's current position and the existing regulatory controls.

Introduction

2. This paper focuses primarily on the food safety and consumer choice aspects of GM foods. It does not address the cultivation of GM crops, except where they impinge directly on food safety matters, as this is the responsibility of other Government Departments.

3. The sale of all novel (including genetically modified) foods is controlled by the EC Novel Foods and Novel Food Ingredients Regulation (258/97). This Regulation lays down an EU wide pre-market approval process. Before a GM food can be approved for sale it must be subjected to a rigorous safety assessment procedure. There is also a requirement to label all foods containing GM material. Details of the regulatory framework are at **Annex 1**.
4. The general Government position has been to make it clear that it does not want to see the UK deprived of any potential benefits that GM foods may bring (such as better nutritional properties, health improvements, flavour, choice, price etc) or become entangled in unnecessary trading disputes, but that it is strongly pro-safety, pro-choice and pro-openness. Its policy is therefore to allow the development and sale of GM foods as long as they have first been rigorously assessed and judged to be as safe as their conventionally produced counterparts and provided that they are clearly labelled. Nevertheless, the Government recognises that the public has worries about the implications of using GM technology for food production purposes. The most common concerns have been summarised in a paper produced by the Government's Chief Scientific Advisor, Sir Robert May, in February 1999 (**Annex 2**). Part of the Government's strategy for addressing such misgivings and for recognising the wider concerns, is to encourage open debate on the issues. A Ministerial Cabinet Committee on Biotechnology and Genetic Modification (MISC6) was also set up by the Prime Minister in Autumn 1998 to co-ordinate the Government's policy on all aspects of biotechnology. The Food Standards Agency is represented on this by the Minister for Public Health.

Background

Safety Assessment

5. The Advisory Committee on Novel Foods and Processes (ACNFP) assesses the safety of all GM foods (see **Annexes 3-4**). It models its safety assessment on procedures initially developed by the FAO and WHO, taking a cautious approach to allow for any uncertainties in the knowledge base. In 1990 these UN bodies convened an expert consultation which recognised the limitations of traditional toxicological test methods when applied to whole foods and recommended that a more structured approach to safety assessment should be developed. The 1990 consultation also formulated the principle whereby the food being assessed is compared with an equivalent conventionally produced one that has an accepted level of safety. This approach was developed further by the OECD to become the concept of substantial equivalence. This concept, although developed for GM foods, is also used in the safety assessment of other foods. It is not a safety criterion in itself, but a structured way of analysing a GM food. Recently the concept has attracted some criticism. In an open debate at the OECD Edinburgh conference, it was recommended that the concept should be reviewed. This month an FAO/WHO expert consultation reviewed and endorsed the concept.
6. In a review of the procedures for the safety assessment of GM foods carried out last year, the Chief Medical Officer and the Chief Scientific Adviser indicated that

they were reassured by the precautionary nature and rigour of the current procedures. Their report (**Annex 5**) included an assessment of the work by Dr Pusztai. Although Dr Pusztai's work was widely regarded as being the trigger for much concern about the safety of GM foods, his work was considered by the ACNFP and the Royal Society to be fundamentally flawed. The potato he was testing was not in any case intended to be developed for sale.

7. To underpin the safety assessment of novel foods the Food Standards Agency has a research budget of approximately £1.5m per year. In considering areas for future research a range of organisations are consulted including the ACNFP and the Medical Research Council. The latter has recently completed a review of possible research on GM foods, which is expected to be published shortly. This endorses the current approach to assessing the safety of GM foods while identifying areas for future research aimed at keeping up with developments in the technology. The Food Standards Agency recently commissioned a pilot study to examine the feasibility of using epidemiological techniques to assess any post-marketing effects of GM foods on public health, recognising that this presents a considerable challenge. It is also funding work to investigate the potential of emerging molecular techniques, such as gene arrays and proteomics, to strengthen the current safety evaluation procedures in preparation for the next generation of GM foods.

Consumer Choice

8. Labelling is seen as a key aspect of providing consumer choice. There are now detailed EU rules for the labelling of foods containing GM ingredients, as well as GM food additives and flavouring substances. Further details of the current labelling requirements are at **Annex 6**. These are based on the principle that all statutory labelling should be capable of enforcement. For this reason, Member States have unanimously agreed the requirement to label only where GM material (novel DNA or protein) is present in a food sold to the consumer. Companies are however free to go beyond this on a voluntary basis, for example, by labelling where ingredients have been obtained from a GM source but where no GM material is present in the final food, or by making a claim that a food is 'GM free'. The European Commission has indicated however that it is working on proposals for rules to regulate this latter activity although at present few, if any, manufacturers or retailers are making direct claims of this type on the labels of the products that they are selling. Most are confining themselves to indicating that they are using only non-GM ingredients, recognising that there are limits to what can be claimed in terms of purity.
9. The Food Standards Agency is committed to ensuring consumers are given clear, easily understood information to enable them to be able to make informed choices about the food they buy. The results of The Better Labelling Initiative launched on 21 January are currently being analysed and will need to be carefully considered by the Agency in formulating its policy on GM foods, when they become available in 3-4 months time. Enabling one group of consumers to exercise their right to choice should not however be allowed to unduly restrict the choice of others.

10. At the present time there is no requirement to label animal feed to indicate whether it contains GM material, although the Government has been pressing the European Commission to bring forward proposals for a novel feeds regulation which would address both the safety assessment and labelling of animal feed material. In the meantime, the Advisory Committee on Animal Feedingstuffs (ACAF) has been reviewing animal feed labelling and has recently undertaken a consultation exercise. ACAF will be considering the results of this shortly.

Openness

11. Last year the Government undertook a detailed review of the advisory committee framework for overseeing developments in biotechnology and the regulatory processes. The aim was to ensure that it was receiving the best possible advice, and that the system was comprehensive and robust, but flexible enough to respond to future developments. A major element of this was a public consultation, undertaken in December 1998.

12. The main conclusion reached as a result of this exercise was that two new strategic biotechnology commissions should be established to strengthen the existing system by providing a focus for issues of public concern to be discussed. The Human Genetics Commission (HGC), which is run jointly by the Department of Health and the Office of Science and Technology, will advise on applications of biotechnology in healthcare and the impact of human genetics on people's lives. The Agriculture and Environment Biotechnology Commission (AEBC), which is run jointly by the Department of the Environment, Transport and the Regions and MAFF, will cover the use of biotechnology in agriculture and its environmental effects. The work of these bodies is intended to parallel that of the Food Standards Agency. Further details of the HGC and AEBC are at **Annex 7**.

13. Recognising the importance of a dialogue between all stakeholders, the UK Government hosted an OECD conference in Edinburgh on GM food safety in February. The conference, which formed part of the OECD's response to a G8 communiqué of June 1999, brought together some 400 participants from more than 40 countries representing governments, industry and civil society organisations. It was particularly notable for the strong participation by developing countries. The Conference was widely seen as a success having brought together all sides of the debate. Many of the speakers from developing countries stressed the importance of the technology to them. An important recommendation from the conference was that an international panel should be established to continue the dialogue and provide governments with robust scientific advice. The UK is currently considering how this might be done in discussion with the other G8 countries. A view as to whether or not to go ahead with this is likely to emerge from the next G8 meeting in July. The report of the conference is at **Annex 8**.

Discussion

Role and Current Position of the Food Standards Agency

14. The Food Standards Agency has a responsibility to deal with two main issues in relation to GM foods. It must ensure that all such foods on sale in the UK have been thoroughly assessed for safety and that consumers are given as much choice as possible whether to buy them or not. The Agency is not directly responsible for assessing environmental issues associated with the production of such foods, nor is it responsible for dealing with wider issues such as the ethical implications of the technology. However, both aspects can impact upon consumer choice. The Agency already has close links with the Department of the Environment, Transport and the Regions, which provides the UK competent authority for the environmental release of GMOs. The Agency will also need to work closely with the AEBC. Indeed the Food Standards Agency Chairman intends to keep in close touch with the chairmen of the AEBC and HGC.
15. Although the Board is not expected to assess individual applications it will need to ensure that the safety assessment process remains firmly based on the best scientific evidence available, is open and transparent, and is underpinned by a sound R&D programme. This is consistent with the Prime Minister's endorsement of a science-based, rules-based approach to addressing developments in biotechnology at the G8 economic summit last year. A case by case approach to new products would appear to continue to be the best way forward. The Board is therefore asked whether it is content to endorse the present safety arrangements based on this approach (and thus the 4 GM products which have been approved and marketed to date - see Annex 1, paragraph 8), whilst recognising the need to keep the assessment procedures under review, so as to take account of new techniques, and thus ensure that public health remains fully protected.
16. It is expected that the Agency will continue to obtain its scientific advice from the ACNFP, which in turn may seek advice from other expert committees such as the Committee on Toxicity. The ACNFP is determined to make its deliberations as open and transparent as possible and the Board will wish to encourage this as well as the continued membership of consumer representatives on committees of this type. The committee currently publishes its agendas, papers and minutes and invites comments from the public and others on individual applications via its website before reaching its decision. It is considering beginning to hold open meetings from the end of this year.
17. The Agency will also wish to ensure that the labelling of GM foods conveys accurate information in a way that is clear and readily understood. However, whilst recognising the desire of some consumers to be informed whenever a food ingredient has been derived from a GM source, even where the ingredient is chemically identical to that obtained from a non-GM source, in reality such a requirement would be extremely hard to enforce. The general difficulty of ensuring the 'purity' of non-GM ingredients derived from bulk commodities, such as soya and maize, has recently been recognised in the setting of an EC contamination threshold for labelling of 1%. There is therefore a finite limit to what can be achieved (although this may ultimately be lower than 1%).
18. In addition to the openness of the approval process for individual GM foods, the Agency will wish to recognise the need for an open and inclusive debate to build

on the initiative of the recent OECD conference. It will therefore wish to welcome the proposal to create an international panel of experts as recommended at Edinburgh, recognising that such a body would be helpful to the Board's future deliberations on GM matters. An important function of such a panel would be to offer an expert international interpretation of emerging scientific findings (but not to assess individual products), to ensure that governments and the public are provided with the facts rather than unsubstantiated and inaccurate claims.

Issues for future consideration by the Food Standards Agency

19. The Agency will wish to ensure that safety assessment procedures reflect the latest scientific thinking and are kept continuously up to date. It will therefore wish to encourage international collaboration amongst the experts, with a strong supporting R&D effort, and to remain in close touch with the work of the ACNFP.
20. The Agency will also wish to ensure that consumer choice is protected recognising that there are limits to what can be legitimately achieved in terms of the purity of ingredients. Clear rules covering the use of the term 'GM free' are therefore desirable and the EC commission should continue to be pressed to make proposals on these as quickly as possible. It should also be pressed to produce proposals for labelling animal feed.

Board action required

21. The Board is recommended to:

- **Note** that extensive legislation on the approval and labelling of GM foods already exists at European level. Since this is occupied Community territory, the scope for national initiatives is limited.
- **Note** that proposed legislation on GM animal feed is awaited from the European Commission.
- **Decide** whether it is content with the existing safety controls and the safety assessment procedures, and therefore with the currently approved GM foods, and identify any areas where it wishes to seek further clarification.
- **Agree** that in deciding its position on the appropriateness of the current labelling requirements, it should await the outcome of the consultations on food and animal feed labelling.
- **Consider** whether it wishes to seek the views of stakeholders on the adequacy of current controls whilst making it clear that there are constraints on the extent of any changes that could be achieved in the short term because of existing EU legislation.

LIST OF ANNEXES

ANNEX 1 - REGULATORY CONTROLS

(i) EC Directives and Regulations

1. There are three main pieces of EC legislation currently in place, which between them cover all stages of the development and use of GM materials. These are:
 - (i) EC Contained Use Directive (90/219) which deals with all aspects of the development of GM micro-organisms prior to their release into the environment;
 - (ii) EC Deliberate Release Directive (90/220) which lays down environmental safety (including human health) controls for the release and marketing of all GM materials capable of reproducing themselves (genetically modified organisms);
 - (iii) EC Novel Foods and Novel Foods Ingredients Regulation (258/97) which covers all aspects of the use of GM technology for the production of foods.
2. In Great Britain the competent authorities for these Directives are the Health and Safety Executive, the Department of the Environment, Transport and the Regions and the Food Standards Agency.
3. Each of the three main pieces of EC legislation requires full safety assessments of the technique or product to be carried out before approval for its use can be given. The initial detailed assessment is made by the member state in whose territory the company first wishes to undertake the work or market the product. In the UK this is undertaken by the statutory Advisory Committee on Releases to the Environment (ACRE) in the case of all applications to release or market GMOs, except food. The FSA's Advisory Committee on Novel Foods and Processes (ACNFP) and the FSA/MAFF Advisory Committee on Animal Feedingstuffs carry out food and feed assessments, respectively. These assessments are then forwarded to Brussels for distribution to the other member states for their consideration and, provided that no objections are raised, approval under the respective Regulations must then be given. If any scientific objections are raised, the matter is referred by the Commission to one or more of the Community Scientific Committees. The member states then consider the issues together in Brussels taking account of the advice from these committees and determine the outcome by qualified majority or, failing this, Council procedure. The consequences of this process are that once a product has been approved for marketing in the EU a member state cannot refuse to accept it in its territory unless new information comes to light indicating that the safety assessment may be invalid. Whilst recognising the need for caution the UK approach is that approval decisions should be based on science.
4. Under the EC novel foods regulation detailed procedures for the safety assessment of novel foods are set out in guidelines developed by the EC Commission's Scientific Committee for Food. These guidelines are intended to ensure that the safety assessment of novel foods is consistent across all member states. They draw upon the structured approach developed by the

UK's ACNFP over many years. The need for animal studies is considered on a case by case basis.

(ii) The National List System

5. Before crops can be planted commercially in the EC a further step that has to be taken in addition to obtaining approval under the terms of Directive 90/220. This is the inclusion of the variety on a National List or the EC Common Catalogue. Under the Seeds (National List of Varieties) Regulations 1982 as amended, which implement various EC Directives, all new varieties of the main agricultural crops (whether conventional or GM) must be grown in official tests and trials, normally for two years, to establish that they are Distinct, Uniform and Stable and have value for cultivation and use. At present there are no GM varieties on the UK National List although two varieties of spring oilseed rape have completed all the tests and trials. They will be considered for National Listing once the marketing approvals which were agreed in Brussels last year, have been formally issued by the Member State that received the original application. Addition to the EC Common Catalogue which normally follows National Listing allows the variety to be planted anywhere in the EU. Again, there are no GM varieties listed as yet. There is at present an agreement between the UK Government, seed producers and others not to grow herbicide tolerant GM crops commercially until farm scale trials to check that there will be no unacceptable effects on the environment have been completed in 2003.

(iii) Pesticides Approvals

6. Finally, as far as legislative controls are concerned, there is a requirement to ensure that all herbicides and pesticides have been specifically approved for the purpose for which they are intended. The main considerations here are efficacy and human and environmental safety. At present there are no approvals for the use of herbicides on GM herbicide tolerant (GMHT) crops in the UK and there would obviously be no advantage in planting these until this clearance is obtained.

NOVEL FOODS ASSESSMENT

7. Up until May 1997, the UK operated a rigorous and wide ranging voluntary approval system for GM foods. Since that time the requirement that all such foods should be assessed for safety before being allowed onto the market has been enshrined in the EC Novel Foods and Novel Food Ingredients Regulation (258/97) which applies to all member states. This requires companies who wish to market new GM products to apply to the Member State in whose territory they first intend to sell the material for a safety assessment to be carried out. That member state then has 90 days in which to reach a conclusion on this after which its report is circulated to all other member states via the EC Commission for their consideration. Each member state then has 60 days in which to study this and raise any concerns that it might have. If these are scientific or technical

and cannot be readily resolved, the Commission will refer the application to the EC Scientific Committee for Food for a further assessment. The outcome of that assessment then forms the basis for the final decision as to whether the product should be allowed onto the market or not. This is reached by the member states acting together under the qualified majority voting system. In this way, a new product is not only assessed by the technical experts in the lead member state but also those in other member states and where necessary, an EC expert committee.

8. The first GM food ingredient, a bakers yeast, was approved for sale in the UK in 1990 (although never marketed). The following year approval was given for the use of chymosin derived from GM microorganisms in cheese production. This source is used to produce the vast majority of hard cheese sold in the UK. The first food derived from a GM crop to be sold in the UK was a tomato paste developed by Zeneca. This product was clearly labelled and accompanied by product leaflets explaining how it was produced. It outsold its conventional counterpart, which was displayed alongside, by a large margin, until Spring 1999. The other two products which have been assessed and are currently on sale are ingredients derived from herbicide tolerant soya and various varieties of herbicide and insect resistant maize.

Animal Feed Position

9. The Commission has been working for some time on a proposed Regulation covering novel animal feedingstuffs including those which are genetically modified. Despite lobbying by member states at Ministerial and official level, the proposal has not yet been presented to the Council and European Parliament and the exact timing remains uncertain.
10. The Advisory Committee on Animal Feedingstuffs (ACAF) is a new independent advisory committee which first met in September 1999. Unlike the ACNFP, ACAF is a broadly based committee set up to look at general issues, such as labelling, as well as assess the implications of new GMOs for human and animal safety via the animal feed pathway. As yet it is still seeking its precise role and mode of working in this area, although it had a helpful joint discussion with the ACNFP in December on certain approaches to assessment. Until the EC novel feed Regulation is agreed, it is likely that dossiers on new GM plants will continue to be referred to ACAF for its recommendations by the Advisory Committee on Releases to the Environment (ACRE) which provides statutory advice on matters falling within Directive 90/220.

Public Information on Novel Food Applications

11. The ACNFP has for several years published agendas, minutes and assessment reports in addition to encouraging applicants to deposit all non-confidential data in the British Library. As from December 1999, when the necessary legislation came into force, the ACNFP has required applicants submitting applications in the UK to agree to the disclosure of non-confidential data. This will be placed on

the ACNFP website the day an application is accepted such that members of the public, and any others with an interest, can submit comments which the ACNFP will then take into account as part of their safety assessment. The first such application was placed on the website on 25 May. The ACNFP's draft opinion on an application will also be placed on the internet inviting further comments before the opinion is finalised prior to sending to other member states.

International Legislation

12. World Trade Organisation (WTO) rules allow trade restrictions to be applied only where this is necessary to protect human, animal or plant health. Measures must be based on sound science and must not discriminate against particular trading partners. All the GM materials currently allowed onto the European market have been thoroughly assessed for safety. For governments to require segregation of GM from non-GM crops or products as a condition of import would be considered a restriction on trade and therefore challengeable under WTO rules. WTO rules do not prevent individual companies demanding the segregation of products they purchase as part of normal commercial transactions. Indeed as previously mentioned the major UK retailers have adopted such an approach when sourcing soya and maize based food ingredients
13. The recently agreed Biosafety Protocol will, when ratified by 50 signatories require that all consignments of commodity crops traded internationally are labelled 'may contain' unless it can be demonstrated that no GMOs are present in a consignment.

ANNEX 2 - GENETICALLY MODIFIED FOODS: FACTS, WORRIES, POLICIES AND PUBLIC CONFIDENCE

A note by Sir Robert May FRS, February 1999

Summary

I think my views are shades of grey rather than the crisp black and white which characterises far too much of the debate on GM foods and agriculture. Our increasing understanding of how living things work, and how they assemble themselves from the instructions coded in their DNA, is offering us opportunities to make a better world -- a world in which we engineer adaptations to harsh environments and defences against pests into our crops, instead of addressing problems with chemicals or other interventions based on fossil fuel energy. I have sketched a personal view, in which I have confidence in our precautions relating to food safety, some doubts about how completely we understand the problem of "escaping genes" (but little apprehension about the likely consequences), and real concern about the way this technology could accelerate existing adverse changes in the countryside (which could, however, be addressed by thoughtful policies to reconcile hi-tech agriculture with maintaining biological diversity). And I have emphasised that the benefits of GM food and agriculture can be not only wealth

creation -- though they can be that -- but even more can be quality of life, provided they are wisely used. I want the UK to remain a leading player, because I believe we can be a force for good on the international stage in this, as we have been in climate change.

Introduction

Around the world today, something like 35 million hectares -- an area roughly one and a half times the size of Britain -- is producing commercial crops of genetically modified (GM) plants. The crops range across soya, maize, oilseed rape, potatoes, cotton and tobacco, and are mostly growing in the USA, Canada and China. The uptake of biotechnology by the agriculture and food sectors in Europe is, by contrast, still at a very early stage though commercial crops of GM maize are growing in Spain and France. No commercial GM crops have been planted in the UK.

This is perhaps surprising. The UK is second only to the USA, and well ahead of other larger countries, in the basic scientific research that is opening new doors in understanding how living things work. From the first recognition of the double helical structure of DNA in Cambridge, to pioneering the sequencing of the genomes of increasingly complicated organisms, the UK has played a disproportionately large role. Our scientists play a major role in developing this science, from basic research into how living organisms work, to specific applications, such as cancer research. In particular, in the international collaboration to sequence the human genome -- letter by letter to read the instruction manual by which we ourselves are constructed -- the UK is doing roughly one third of the work. Furthermore, our pharmaceutical and healthcare industries are among the leaders in beginning to apply this new knowledge to create better drugs, treatments and vaccines, and to think ahead to countermeasures to combat the rising global threat of infections which are multiply resistant to today's antibiotics.

Against this background, why has Europe in general, and the UK in particular, been relatively slow to exploit the new biotechnology in agriculture and foods? And why are so many people so much more worried here than, for example, in the USA?

Part of the answer must, I think, lie in our recent experience with BSE. In essentials, the BSE epidemic among cattle in the 1980s was caused by a rogue prion (a kind of protein, smaller than a virus) whose origins remain unclear: perhaps a rare mutant; perhaps something that has been around for a long time but occurring in so few animals as to escape notice. Whatever its origins, the numbers of animals affected by this prion were hugely amplified by the relatively recent practice of collecting the left-over bits from the abattoir and putting them into the meal fed to their relatives back on the farm. This practice came from an understandable wish for efficiency, making better use of all available protein. In short, BSE in animals and consequently new variant CJD in humans arose as an unintended effect of changing agricultural practice, arguably without sufficiently wide-ranging consultation about the possible consequences. Today it overshadows all discussion of GM foods in the UK, and in Europe more generally.

Lessons have been learned. We need to have much better lines of traceability from food production to the table. We should allow consumers maximum information and choice about what they buy through clear labelling. And we must test. No-one was looking out for untoward effects in cattle. In the case of GM food we are testing for unexpected and unwanted effects on human health and on the environment.

So how sure can we be that no nasty surprises lie in wait in GM foods? The worries can be grouped under three broad headings. First, that the genes put into GM foods -- the new instructions put into their DNA which effectively tells the plants how to construct themselves -- may unwittingly create health hazards for the consumer. I would call this the "BSE-type" worry. Second, there is the possibility that genes incorporated into a crop to make it resistant to pests or diseases or herbicides may leak out, through cross-pollination or otherwise, into the wider countryside, creating "superweeds". By the same token, "marker genes" are sometimes put in to enable us to identify and keep track of GM plants. Often (and arguably foolishly in my view) these marker genes are antibiotic-resistant, so there could be a risk that humans could acquire these antibiotic-resistance genes from their food, thus accelerating the already existing, and very troublesome, world problem of increasing resistance to today's antibiotics. I would call this worry about unintended consequences elsewhere in the food chain the "DDT-type" worry. Third, the motivating idea in many GM crops is that no weeds, wildflowers, insects or birds should be able to compete with or consume them. This is an understandable goal from the narrow view of producing food for humans. But it is bad news for biological diversity in the countryside. In other words, many GM crops will intensify and accelerate changes in the countryside which already exist and which trouble many of us, including me. So I could call these concerns "hedgerow-type" worries.

I will now consider each of these three categories of worry in turn, and conclude by emphasising -- present worries being acknowledged -- some of the potential long-term benefits of GM foods.

A fourth kind of worry should be recognised, even though I will not deal with it. This is the argument that says that God did not intend us to meddle with nature in this way. In my view this argument, pursued to its logical conclusion, might see us as still being small, roving bands of hunters and gatherers. But even when we were, we were busy changing our environment, not least in killing off big mammals. Changing circumstances, and our own responses to such change, seem to be built into our history, no matter how you look at it.

Genetic Modification: The Underlying Science

Genes are the instructions that give organisms their characteristics. These instructions are stored in each cell of every living organism in a long string-like molecule called DNA. The full set of instructions is called a genome. All organisms have genomes of varying sizes; for instance the human genome has an estimated 60-100,000 genes; most plants have about 20,000; the nematode worm (a microscopic creature) has about 18,000; and the single-celled *Escherichia coli* bacterium has just over 4,000.

Our knowledge of genetics allows the identification of individual genes, and often understanding of their specific properties. The technique of genetic modification (also known as genetic engineering, and genetic manipulation) allows those individual genes to be cut out of the genome of one organism and pasted into the genome of another.

Deoxyribonucleic acid (DNA) is the genetic material of all plants, animals and bacteria and of many viruses. It is made up of just four building blocks called nucleotides (or bases) - Adenine (A), Cytosine (C), Guanine (G), and Thymine (T). It is the linear sequence of these bases that contains the genetic information. Rather like Morse code, only instead of two elements (dots and dashes) the DNA code has four - A, C, G, T. DNA usually exists as two separate strands, twisted together in the well known double helix pattern. The genetic difference between species, and organisms within a species, lies in the different ordering or sequence of these bases and the genes that they form.

In the first genetic modification experiments, which took place in the mid 1970s, synthetic human genes were combined with genes from a bacterium. Many apprehensions of possible dangers were raised at this time. They were carefully addressed by the scientific community (in particular at a noted conference in Asilomar), and none of these conjectured problems have actually arisen. Later that decade, researchers learned how to insert genes into fungi and yeast. In the 1980s, they found ways of putting foreign genes into the cells of plants and some animals. In the 1990s, the first experiments to insert new genes into human cells and tissues were developed.

In principle, genetic modification allows researchers to move genes between all living creatures. In practice, so far it has only been made to work in a few animal, plant, and microbial species – usually organisms that humans have used for many years in agriculture, food manufacture, and industry.

What is perhaps most surprising about genetic modification methods is that they work at all. How is it possible that genes from one organism can be processed by an unrelated organism? The answer lies in the fact that DNA has the same basic characteristics in all organisms. Because all DNA is composed of the same basic ingredients, a gene pasted from, for example, a simple organism like a virus can in principle function in the same way in a more complex organism like a plant.

Modern computer databases containing huge amounts of sequence data from large-scale genome projects are making the task of identifying genes with particular desired characteristics (e.g. the gene that codes for production of vitamin C in citrus fruit) far easier than in the past. Once identified and isolated, gene sequences can be cut and pasted into bacteria, which then manufacture multiple copies of the genes. This enables, for example, the production of essential medicines like insulin to be produced from GM bacteria rather than from animals. Such insulin is produced in a cleaner, more controllable environment than was previously the case. Other sequences are often introduced at this stage, for instance, selective marker genes conferring resistance to one or more antibiotics are often linked to the trait genes to allow researchers to pick out only those bacteria that have successfully received the new gene sequences. Extra regulatory sequences may also be added at this stage,

to control the gene's expression i.e. whether it should function only in certain parts of the new host, or 'switch on' at a certain stage of its development.

Once the gene is complete within the 'carrier', it needs to be inserted into the new host. For GM plants and animals, this stage is complicated by the need to introduce the genes into all the cells in the organism. This can be achieved by inserting the prepared genes into a single cell of the new host. This single cell can then be cultured into a whole organism in which all the cells contain a copy of the introduced gene (the process works similarly if a gene is removed instead of added). A number of methods are used to insert genes into cells. Bacteria and yeasts are often encouraged with chemical and electrical treatments, and disarmed viruses can be used to carry genes into animal, plant and human cells. There are also direct ways of taking genes into cells: by injecting them with very fine needles or by forcing them in aboard tiny metallic bullets. Amazingly, these techniques do not damage the cells.

Concerns about the Safety of GM Foods

The non GM cereal crops we grow today are the result of several thousand years of artificial selection. Only an expert can recognise their relationship to their wild ancestors which still grow in the Near East and elsewhere. The past 50 years or so have probably seen more changes than the past thousand, as increasingly sophisticated artificial selection has created the Green Revolution in rice, cereals and other crops that underpin high intensity agriculture around the world. Without these improvements in agricultural yields, we could not feed the world's 6 billion inhabitants today.

Artificial selection essentially works by cross breeding to enhance desired qualities: short stalks, more grain (seeds), resistance to disease, and so on. But the methods, based on the recombination and reshuffling of genetic material that occurs in sexual reproduction, have a necessarily scattershot component. For example, when we eat non GM tomatoes today, we are eating material that carries disease resistance genes which have been bred in from wild relatives of tomato, along with two thousand or more other genes unavoidably brought in at the same time and which are not the same as in the earlier cultivated plants.

By contrast, the revolution in plant science over the past ten years derives from an increase in understanding how cells and organisms work at the molecular, biochemical and physiological levels, along with the development of techniques which allow us to transfer genes from one plant species to another. This means that we can transfer two or three precisely identified genes to a plant's typical total of around 20,000 genes (the functions of most of which are not understood). The added genes are extremely well understood. In this sense, the production of new GM plants is a much more controlled and understood process, with less potential for unforeseen consequences, than conventional artificial breeding.

However, GM techniques also enable us to insert particular genes from a very different species -- a bacterium, an insect, a fish -- into a plant's genome. The more we learn about the molecular history of life on earth, the more we find genes from one species unexpectedly popping up in a vastly different species, but even so the controlled transfer of a gene from one branch of the tree of life to a very different one

raises questions. In other words, on the one hand GM techniques mean we have a much clearer understanding of exactly what we are doing than is the case with the much larger transfers of genetic material in artificial breeding, but on the other hand we can do some things with the new techniques that would be very difficult with the old ones.

This is why we need a carefully thought through process of review and regulation before any new GM product can come to market. We need first to be sure that we understand fully all the effects of the changes we have introduced. Rigorous EU legislation governs such assessment, and in the UK new foods need the approval of our independent Advisory Committee on Novel Foods and Processes (ACNFP).

The questions posed by Dr Pusztai's work at the Rowett Research Institute are illuminating here. In essentials, Pusztai claims to have produced GM potatoes which incorporate a gene for lectin, and which damaged the liver and immune system of rats fed on them. From these results, Pusztai and members of the International Institute for Science in Society draw sweeping conclusions about the unpredictability and safety of GM foods. Setting aside the gross violations of universally accepted scientific procedure here (Pusztai's work has never been submitted for peer review, much less published, and so the usual evaluation of confusing claim and counter-claim effectively cannot be made), suppose the studies and results were exactly as asserted. Would this call the present regulatory system into question? I think not. Lectins are known to be toxic to some pests, and so one would look very carefully at any proposal for GM foods modified to produce them. The Pythagorean cult in Ancient Greece would not eat beans, and we now conjecture that this was because the lectins they contained were toxic unless cooked. If there were a possibility that a gene coding for a substance that might be toxic to humans might pass into the human food chain, then I believe our present procedures would identify it and prevent it from doing so. This particular incident can be roughly characterised by saying, if I were to mix cyanide with Vermouth, and found the resulting cocktail unhealthy, I would be silly to draw the conclusion that I should never mix drinks.

One final point is important here. In many cases, the new genes in the GM food are simply not present in that part of the plant which ends up on the supermarket shelf. Oil from GM soya is an example. The GM soya has resistance to particular herbicides built into it. Farmers in the USA and elsewhere have rapidly switched to it -- a large proportion of the world's soya oil is already from GM crops -- because it requires less expenditure on herbicide to prevent weeds overrunning the crop, and the herbicide can also be more effective and less toxic. Refined oil extracted from the soya beans, however, does not contain any detectable remnant of the genetically modified DNA which coded for its construction. Although traces of protein may be detectable in unrefined oils, the refining process removes such traces. Conversely, in the case of lecithin, an additive which is a mixture of generally unrefined acids from soya, DNA is indeed detectable. The European Commission is therefore addressing the question of labelling lecithin derived from GM soya.

Here again is a ready source of confusion for the nonexpert. Many of the products of GM crops have, by the time they reach the consumer, been processed in ways which effectively remove all of the modified DNA. The soya oil has, in this sense, lost all memory that a herbicide was engineered into another part of the plant from which

it was extracted. It can be argued that there is no scientific need for such products to carry a GM label.

The UK Government's policy is, of course, to label GM foods, so that consumers can choose. My view is that it is certainly right to label foods containing GM DNA. But the case for labelling refined oils derived from GM soya or oilseed rape, which contain no DNA and no memory of genetically modified instructions for the functioning of other parts of the original plant is, I think, debatable. The question is further complicated by the fact that, although the Laboratory of the Government Chemist could not find protein or DNA in refined soya oil, in some other products with "no DNA remaining" there may be minute amounts residually present, maybe one tenth of one percent or less; this is arguably the case with some food products that are marked "GM free". This is an issue on which I would like to see further public debate.

My conclusion is that there can be questions of health and safety associated with some GM foods, particularly if we introduce genes coding for production of toxins against certain kinds of pests. But, partly because GM foods are produced by a much more targeted and controllable process than conventional plant breeding, I think a strong and well planned regulatory structure can be thoroughly relied on. But the question of public choice and public confidence is, I think, paramount. Hence I strongly believe we should label foods that are GM in a meaningful sense, even though we may feel sure that our regulatory processes make it wholly unnecessary on safety grounds.

Concerns about "Escaping Genes"

A second class of worries centres on genes, which were inserted into a GM crop, escaping into other organisms, to produce unintended problems. One example might be GM crops with herbicide resistance accidentally interbreeding with wild relatives to produce "superweeds". Another possible example is antibiotic-resistance genes which were engineered into a GM crop as "marker genes" managing to escape into humans, or elsewhere in the environment, in ways which would further accelerate present worrying trends towards resistance to the current armoury of antibiotics.

There are two questions here. One is whether genes may escape in this way. The other is whether they are likely to cause significant problems if they do.

To the first question, the answer is that such escapes are possible. They can, of course, also occur with new varieties produced by artificial breeding. Their likelihood depends in complex ways both on the molecular genetic details and the ecology and environmental setting in which the GM crops find themselves. This is, in part, why we need experiments in the field -- that is, in realistic environmental settings (and not just in greenhouses) -- to learn more about patterns of movement and possible interbreeding of GM pollen, seeds, and so on. It is a pity that many such studies to learn more about these questions have been impeded by eco-activists. My personal view is that, although the safety issues discussed above have received much attention, ecological aspects of possible "escapes" are less thoroughly understood. It is, however, one of the risks assessed by the United Kingdom's Advisory Committee on Releases into the Environment (ACRE) as part of the regulatory process. Under

European rules, approval has been given in principle for commercial planting of a small number of crops. But Ministers have asked, and the companies have agreed, not to proceed with commercial planting for at least a year while more thorough studies are carried out.

If such escapes occurred, are they likely to cause problems? In the case of "superweeds", I think not. For one thing, such escapees would be very one-dimensional in their superiority. Like the GM crops they borrowed from, they would be resistant to a restricted range of herbicides, and could if needed be zapped with alternatives. Even so, neither the industry nor the public wants such transiently super weeds.

In the case of antibiotic resistance marker genes, my first comment is that any increase in general antibiotic resistance associated with escapes from GM crops will be a drop in the bucket compared with overprescription (or uninhibited availability in many countries) for human use coupled with widespread use on farms (half of all antibiotics sold in the UK go to farm animals). But, again, we should nevertheless be concerned to prevent such accidental releases from GM crops. Here the discussion necessarily involves specific details.

For example, the tomato approved for use in the UK contains an antibiotic marker gene. The promoter gene in this case is of plant origin. This means that the antibiotic resistance gene cannot be switched on in an animal or human environment, nor in an animal or human gut where bacteria are present. The gene, moreover, codes for kanamycin which is an antibiotic not used in humans and only to a limited extent in veterinary medicine. For all these reasons, the ACNFP had no reservations in giving approval to this tomato, which has been successfully marketed in a tomato paste.

Recent discussion in the European Community about the Spanish proposal to approve commercial planting of GM cotton is interesting. The UK was content that this crop would not pose a danger to the environment in the field. But, as a marker gene, the plant carried a gene resistant to streptomycin (used in the treatment of human infections). Cautious against the possibility of this gene escaping into the food chain as a result of the use of cotton as an animal feed, the UK voted against release and will continue to do so.

Recent developments have made it possible to use alternative "marker gene" systems, which do not use genes for antibiotic resistance. As this becomes more common practice, it will reduce this particular category of worry.

More generally, there could be a more diffuse anxiety that some "new" gene in a GM crop might escape into some other plant or animal, and become incorporated into its genome, with unforeseeable effects. Given the specific and targeted nature of the genes inserted into GM crops for very precise purposes, I think this is exceedingly unlikely. It is worth noting, furthermore, that medical researchers have been trying to develop techniques for inserting genes into cells in the bodies of humans for some time, so far with limited success. A recent Royal Society report says "we are not aware of any evidence for transfer of intact genes to humans, either from bacteria in the gut, or from foodstuffs such as potatoes, wheat or chickens, despite daily

consumption of DNA in the diet". The question of accidental wider release remains, however, a question for ACRE consistently to keep in mind.

So-called "terminator technology", the ability to create sterile plants that cannot cross with one another or with wild species in the field, may be a helpful tool to ensure that escape does not occur. But I recognise that there are other concerns about the financial impact on farmers, particularly those in the Third World, who would be unable to save seed from plants modified this way.

Wider Concerns about the Nature of the Countryside

Since the dawn of the agricultural revolution, some ten thousand years ago, humans have been trying to do a better job of preventing weeds ("plants in the wrong place"), pests and diseases competing with us for them. In medieval times, a rough rule was that for every three seeds that grew, we ate one, put one away for next years crop, and lost the third to pests. Today we do a lot better, but around the world we still lose roughly one third of all our crops to other creatures.

The past few decades have seen great changes in agriculture in the UK and elsewhere. High intensity agriculture has increased yields and efficiency, but has correspondingly made for great changes in the countryside. Setting aside emotional preferences, one thing stands out: these agricultural changes are all in the direction of realising the ages-old dream of growing crops that no one eats but us. This has obvious consequences for the invertebrates, mammals and birds that also depend on the fields we use. The Royal Society for the Protection of Birds (RSPB) and others have documented dramatic declines in many bird populations, and although the evidence for corresponding effects on invertebrate and plant diversity is less well documented, I nevertheless find it convincing.

The thrust of GM crops is, entirely understandably, to accelerate this trend. Genes for resistance to herbicides, and for resistance to pests and pathogens, may lead to fewer chemicals being sprayed all over the countryside. But the goal is still to become ever more efficient in making sure that nothing eats our crops except ourselves. These concerns are recognised by ACRE, which will in future consider wider environmental issues when assessing approvals. They have published a paper setting out their concerns and have set up a sub-group to advise them on these issues.

In short, there are real social and environmental choices to be made. On the one hand, most Britons have real affection for the countryside, regretting many of the changes it has already undergone, and not wishing to experience a truly Silent Spring. On the other hand, in a smaller and more competitive world, we need a competitive and efficient agricultural sector (in which I hope organic farming will continue to expand as a niche market).

I believe we need to think carefully how these apparent irreconcilables can be reconciled. I hope the answer will not be further loss of biological diversity, and it cannot realistically be a UK retiring to an Arcadian enclave. We will need to think carefully how to do a better job of reconciling changing agricultural practices with

more targeted use of land: hedgerows, headlands, protected areas, and eventually fewer chemicals as we use GM crops not primarily to enrich an industry but deliberately to improve the environment. These, in essence, are the concerns being expressed by English Nature and others. They are not about safety as such, but about much larger questions of what kind of a world we want to live in.

Regulatory Framework

I have referred above to some UK committees of independent experts, with responsibilities for particular aspects of biotechnology. More generally, the UK Government is advised by fifteen or so committees of independent individuals, some (like the Advisory Committee on Releases to the Environment) comprising specialists to deal with relatively technical questions, and others (like the Human Genetics Advisory Commission) having a diverse membership to deal with larger ethical and other public concerns. The Prime Minister set up a new Cabinet Committee last year to oversee developments in biotechnology -- relating both to health and to food and agriculture -- and to co-ordinate the Government's approach to it. This committee has begun a thorough evaluation of the UK framework of regulatory and advisory committees, to make sure that we have no gaps, unnecessary overlaps or inconsistencies, and also that we have the right balance between technical advice and wider ranging examination of issues of public policy and ethics. We need to be sure that the system is sufficiently flexible to deal with a rapidly developing subject. In addition, the UK Office of Science and Technology (OST) is conducting a Public Consultation in the Biosciences to learn more about public attitudes and concerns, from a widely representative sample; the Consultation recognises that "the public" is a very heterogeneous entity, whose views often tend to differ from those of particular interest groups.

Some of the decisions about biotechnology are governed by European Commission laws and regulations. For example, the final decision on the approval of Novartis' GM maize was made on the basis of evidence from the EU scientific committee, rather than those of member states. In addition, World Trade Organisation (WTO) rules can constrain an individual country's action. WTO rules would be invoked, for example, if a European country sought to prohibit imports of GM soya and non GM soya, mixed in unknown proportions, from the USA. In these international fora, with true British empiricism, the UK seeks to emphasise safety and a precautionary approach, while recognising the benefits that these new technologies can bring.

Potential Benefits

Given that high intensity agriculture in Europe, encouraged by its Common Agricultural Policy, currently produces food surpluses, why not just opt out of the biotechnology revolution? Not only is this infeasible and scientifically unjustified, but it is highly undesirable, for at least two reasons.

The first potential benefit is familiar. There is a huge potential market for new GM "agrifood" in Europe. This new industry is just emerging, the fruit of advances in basic research to which the UK has, as in other areas, made contributions out of all

proportion to its size. Having laid the foundations, are we once again -- as in electronics, liquid crystal displays, and so much else -- going to see others cash in on our cleverness? For anyone concerned with the future state of the UK economy, this is a hugely important question.

This argument is, however, a two edged sword. The agrifood companies are, understandably, motivated by their wish for commercial success. Since they must convince farmers to use their products, developments are likely also to favour farmers' interests, at least in the short run. But there is no guarantee that these economic processes will always act in the long-term interests of consumers, or indeed of the kind of diversified farming industry most of us want to see in the UK. That is why the Government's role in regulating is so important. The commonsensical person in the street recognises this, and it adds a patina of distrust to perceptions already recently soured by BSE.

The second kind of potential benefit from GM agriculture is less commonly discussed. I think this "quality of life" argument is, however, of even greater importance in the long run than the more familiar "wealth creation" arguments.

Today's intensive agriculture is not sustainable in the long run. In developed countries, we typically spend ten calories of fossil fuel energy, in various ways, to put a calorie of food on the table; a century ago this ratio was one to one, and in hunter-gatherer times was 0.1 to 1. At least half the atoms of phosphorus and of nitrogen incorporated into new plant material around the world today comes from fertilisers, rather than by natural biological processes. But we cannot turn back the clock, because we could not feed today's global population, much less tomorrow's, with yesterday's agriculture. Increasing food production has so far kept pace with increasing populations by advances in higher yielding crops -- the Green Revolution -- with their attendant need for fertilisers, chemical pesticides, and the like, along with their adverse and unsustainable impacts on water supplies and biological diversity. Against this background, the world population continues to grow, driven by the momentum of the children already born. Part of the solution lies in better distribution -- it is obscene that Europe produces surpluses while others starve -- but in the longer term we need to bioengineer crops which work with nature to reduce the need for intensive use of chemical fertilisers, pesticides, herbicides and fungicides. This is what the UN Food and Agriculture Organisation (FAO) had in mind when it recently spoke of GM agriculture's "actual and potential possibilities of increasing food supplies and alleviating hunger". We want this bioengineering increasingly to have a Third World orientation, rather than being driven solely by First World commercial forces (the development of "terminator technology", aimed at ensuring that seeds of new GM crops are infertile, is understandable in terms of profit motives, but it highlights the tensions between First and Third World interests). Realisation of these potential longer term benefits is, I think, unlikely to come from commercial forces alone. As in climate change, internationally co-ordinated political leadership will also be needed.

ANNEX 3 - EC NOVEL FOODS REGULATION SAFETY ASSESSMENT PROCEDURES

1. The safety assessment undertaken by the ACNFP and its counterparts in all other EU member states is based where possible on the concept of substantial equivalence. This was formulated by the World Health Organisation and is widely used as the basis of food safety assessments across the world, including in the USA. Substantial equivalence is a framework for assessing the safety of a novel food. It is not a safety assessment itself, but a tool to aid the safety assessment process. It is used to help identify differences between a GM food and its conventional counterpart including both intended and unintended changes, so that these can then be examined in detail.

2. All novel foods are scrutinised in considerable detail, far more so than has been done for conventional foods. Animal feeding studies are required where they are likely to yield meaningful information. In May 1999 the approach to the safety assessment of GM foods was reviewed in detail by the Government Chief Medical Officer, Prof. Liam Donaldson, and the Chief Scientific Adviser, Sir Robert May, who declared themselves satisfied with the rigour of the procedures being followed whilst recognising the fact that genetic modification is still a comparatively young science (see annex 5).

3. The European Commission has published detailed guidelines to accompany the novel foods regulation. These are closely modelled on those developed by the ACNFP and set out the data required to support an application and the way in which member states should assess the safety of a novel food. They are intended to ensure consistency in safety assessments regardless of which member state receives the initial application.

Who assesses safety in the UK?

4. All novel food applications are assessed by the Advisory Committee on Novel Foods and Processes (ACNFP). The ACNFP is made up of independent experts appointed by Ministers. Members are appointed to ensure that a broad spectrum of relevant scientific expertise is represented on the committee; and they are drawn from universities and research establishments. None of them are employed by industry. All interests are published in the Annual Report. There are also two lay members advising on ethics and consumer affairs. The Committee publishes its agendas, minutes and papers and holds open meetings where appropriate.

How does the ACNFP conduct the safety assessment of a novel food?

5. The safety assessment of novel foods by the ACNFP is based wherever possible on a comparative approach in which the novel food is compared with an existing counterpart, which it may replace in a diet. Where such a counterpart exists, as a starting point the safety assessment involves the application of the concept of substantial equivalence, which allows similarities and differences between a novel food and its conventional counterpart to be identified. Any differences undergo a

detailed examination in order to establish whether the novel food is as safe as its conventional counterpart.

6. The concept of substantial equivalence was formulated by the World Health Organisation and developed by the Organisation for Economic Co-operation and Development. It is an internationally acknowledged approach to the assessment of food safety, particularly foods produced by modern biotechnology, and is used by expert assessment bodies world-wide. It has recently been reviewed and endorsed by a FAO/WHO expert consultation.

Which products have been approved for food use in the UK?

7. The only GM food products on sale in the UK are a tomato paste (now withdrawn from sale) made from tomatoes modified to delay softening during ripening (approved in 1995), a herbicide tolerant soya (also approved in 1995) and an insect tolerant maize (approved in 1996). The GM soya and maize are used in a wide range of processed foods and have been approved as for all sectors of the population including babies. Some cheeses and other products are made using enzymes produced from GM micro-organisms but the foods themselves do not contain any GM material.

ANNEX 4 - COMPOSITION OF THE ACNFP

Chairman

Professor J Bainbridge OBE, BSc, PhD, Grad.Cert.Ed(Tech), CBiol, MiBiol, SOFHT. School of Science and Technology, University of Teesside, Middlesbrough.

Members

Professor P J Aggett MSc, MB,ChB, FRCP(L)(E)(G), DCH. (Nutritionist)
Head of Lancashire Postgraduate School of Medicine and Health.

Dr Philip Dale BSc, PhD, CBiol, MiBiol. (Molecular biologist/plant geneticist)
Research Group Leader, Genetic Modification and Biosafety Assessment, John Innes Centre, Norwich. Honorary Reader, University of East Anglia.

Dr M J Gasson BSc, PhD. (Molecular biologist) **Deputy Chairman**
Head, Department of Genetics and Microbiology, Institute of Food Research, Norwich.

Dr J Heritage BA ,DPhil, CBiol, MiBiol. (Microbiologist)
Senior Lecturer in Microbiology at the University of Leeds.

Professor D A Ledward MSc, PhD, FIFST. (Food technologist)
Professor of Food Science, University of Reading.

Reverend Dr M Reiss BSc, MA, PhD, FiBiol. (Ethicist)

Senior Lecturer, Homerton College, University of Cambridge.

Mrs E Russell BSc.
Consumer Representative.

Professor I Rowland BSc, PhD. (Nutritionist/toxicologist)
Director, Northern Ireland Centre of Diet and Health at the University of Ulster;
Coleraine.

Professor T A B Sanders BSc, PhD, DSc. (Nutritionist)
Head of Department of Nutrition and Dietetics, Kings College, London.

Professor H Sewell MB, ChB, BDS, Msc, PhD, FRCP (L) (G), FRCPATH, F.Med.Sci.
(Immunologist) Head of Immunology , Faculty of Medicine and Health Science,
University Hospital Medical School, Nottingham.

Dr N A Simmons CBE, FRC Path, FIFST. (Ex officio member from ACMSF)
Emeritus Consultant in Microbiology, Guy's and St.Thomas' Hospital Trust, London.

Professor R Walker PhD, CChem, FRSC, FIFST. (Toxicologist)
Professor of Food Science, University of Surrey.

Professor J Warner MB, ChB, DCH, MRCP, MD, FRCP, MRCPCH, FRCPCH.
(Allergy expert) Professor of Child Health at University of Southampton.

Professor H F Woods BSc, BM, BCh, Dphil, Hon.FFOM, FIFST, FFPM, FRCP
(London & Edin) . (Ex officio member, Chairman of COT)
Head of Department of Medicine and Pharmacology. Royal Hallamshire Hospital,
Sheffield.

Annex 5 - HEALTH IMPLICATIONS OF GENETICALLY MODIFIED FOODS

Authors: Professor Liam Donaldson & Sir Robert May
CMO/CSA REPORT, May 1999

EXECUTIVE SUMMARY

REMIT

1. We were invited by the Ministerial Group on Biotechnology (MISC 6) to produce jointly a paper on the health implications of genetically modified (GM) food.

SCOPE OF OUR REVIEW

2. We have examined the process involved in genetic modification of food, the areas of human health which could be affected, the safety and regulatory mechanisms which are in place and the need for further research.

FINDINGS

3. In seeking to assess possible hazards to human health arising from GM foods, the main issues which need to be considered are:

- whether there are any inherent hazards in the genetic modification process itself;
- whether the products (ie the food itself) might be harmful; and
- whether GM food given to animals which are then eaten by people could pose a hazard to human health.

4. There is also the question of whether GM technology could lead to environmental change which had a secondary effect on human health. This is beyond the scope of this paper which considers the possibility of direct effects upon human health.

5. We identify key aspects of health which would need to be monitored if effects on human health were to arise. These issues are considered in the paper together with the likelihood of serious risks occurring. We also consider the issue of population surveillance to detect any unexpected effects on human health over the long-term.

6. The main measures to provide safeguards against any real or hypothetical risks are: rigorous pre-market assessment of safety; research to improve understanding of the science of genetic modification of food; and health surveillance to provide reassurance against any unexpected adverse effects on health.

CONCLUSIONS

7. Our key conclusions are as follows:

- Many of the issues raised by foods resulting from genetic modification are equally applicable to foods produced by conventional means. For example, potential nutritional imbalances or allergic effects could occur from either type of food.
- There is no current evidence to suggest that the GM technologies used to produce food are inherently harmful.
- We are reassured by the precautionary nature and rigor of the current procedures used to assess the safety of individual GM foods. This process could be strengthened by the development of a health surveillance system.
- Nevertheless, nothing can be absolutely certain in a field of rapid scientific and technological development. Genetic modification is a young science and there is a need to keep a close watch on developments and to continue to fund research to improve scientific understanding in this area.
- We welcome the recent moves to improve the openness of the regulatory procedures to public scrutiny and would encourage further such moves to help to inform public debate on the issues relating to the health implications of GM foods.

RECOMMENDATIONS

8. We make the following recommendations:-

Tracking research and acting on new evidence

Government advisory bodies should continue to closely monitor development in scientific knowledge and regulation on an international basis and provide advice on any fresh action which they consider necessary.

Promoting high standards of regulation

The United Kingdom's current system of regulation of GM food technology and other novel foods is rigorous. We propose that the Government should offer its expertise and use its influence to promote high standards of regulation internationally.

The need for a continuing research strategy

Government should continue to fund research to improve scientific understanding and to fill gaps in current knowledge. We propose that the Government should invite the Medical Research Council and other major research bodies to participate in the further development of this research strategy. We propose that before any new research is acted upon by Government, it must have been through the standard peer review process to ensure that it has scientific credibility. Government's own response to new data should be made in line with the *Guidelines on the Use of Scientific Advice in Policy Making* to allow the full scientific merits of new research to be assessed.

Instituting population health surveillance

The development of robust population health surveillance in relation to consumption of GM foods is essential to ensure that Government is able to respond rapidly should any unexpected effects occur. The Advisory Committee on Novel Foods and Processes and the Medical Research Council are already discussing how this might be done. As part of this, consideration also needs to be given to the establishment of a national surveillance unit to monitor population health aspects of genetically modified and other types of novel foods. Surveillance could be used to examine trends over time to detect any early changes in the incidence of adverse health outcomes, whilst recognising the difficulties in establishing causal relationships.

Antibiotic resistance marker genes

The use of alternatives to antibiotic resistance genes as part of the GM process is already stated good practice by the Advisory Committee on Novel Foods and Processes (ACNFP). We recommend that those who are developing foods using genetic modification should be encouraged to phase out the use of antibiotic resistance marker genes as soon as is feasible.

CONSIDERATION OF THE PUBLIC HEALTH IMPLICATIONS OF GENETICALLY MODIFIED FOODS

PURPOSE

1. The purpose of this paper is:
 - i) To review the public health implications of consumption of genetically modified (GM) foods and food ingredients;
 - ii) In particular, to consider the *hypothesis* that the use of the recently developed technology in food might be harmful to human health;
 - iii) To review the process of genetic modification and to evaluate the possible hazards at each stage of the process; and
 - iv) To describe how the safety of individual GM foods are assessed in the UK and Europe, in comparison with foods derived from traditional plant breeding.

2. The first part of the paper explains the nature of genetic modification, lists some examples of how it has been used so far, and then describes in more detail how the modification is carried out. The second part of the paper assesses from first principles the theoretical risks to human health and describes some particular examples of health concerns, followed by a detailed description of the current safety assessment procedures used in the UK. This is followed by a description of current and future research on GM food issues and then a section with conclusions and recommendations.

THE NATURE OF GENETIC MODIFICATION

3. Humans have been altering the genetic make-up of animals and plants for centuries. Selective breeding has been directed towards producing desirable characteristics for a variety of reasons: for example, to increase yields, modify the food quality and content (starch, protein or lipid) and to confer resistance to disease. For many years, the genetic make up of seeds has been altered by exposing them to radiation. This causes mutations which lead to new characteristics, which can then be selected and bred on to produce desirable characteristics.

4. The difference between practices like these and the modern approach of genetic modification lies in the way in which humans can now influence these processes of development, growth and yield in the animal and plant kingdom. With the dramatic increase in our basic understanding of the genetic make-up and biochemistry of living organisms, we are now in the position to apply this knowledge in a more considered manner to plant and animal improvement for agriculture and food purposes.

5. The laboratory processes that are used to manipulate this genetic code can be likened to the process of cutting and pasting. Strands of DNA, the basic chemical of life, which are found in the nucleus of all organisms, and which produce a particular effect in one living organism, can be 'cut' out and then 'pasted' into the nucleus of another living organism. The genetic strands are 'trimmed' so that only a precise, fully defined piece of DNA is pasted into the recipient organism.

6. Apart from the fact that the process uses advanced molecular techniques, there are two basic differences between modern genetic modification and traditional animal and plant breeding methods, which are:

- i) Genetic modification enables single, well defined genes to be isolated and transferred, whereas with traditional methods many thousands of genes are 'crossed' at one time.
- ii) Genetic modification allows the introduction of a desired gene from one plant species into another. In addition genes can also be introduced from other organisms such as micro-organisms and animals.

USES OF GENETIC MODIFICATION

7. Genetic modification in the laboratory was first reported in the early 1970s. Since then a wide range of applications in agriculture, medicine, the environment, food production, the manufacturing industry and research have been developed. A number of examples are listed below:

8. In the agricultural area:

- Herbicide tolerant crops
- Insect resistant crops
- Virus resistant crops

9. In the field of medicine:

- Insulin to treat diabetes mellitus
- Production of human growth hormone
- Production of blood clotting factors VIII and IX
- The treatment of cystic fibrosis
- Research into human and animal diseases.

10. In other areas:

- Environmental clean up of oil spills
- Treatment of contaminated land and water
- Manufacture of useful chemicals such as enzymes
- Plants providing renewable sources of industrial chemicals

Genetically modified foods

11. Genetically modified food is defined in the EC Novel Foods Regulation as "a food which is, or which is made from, a genetically modified organism" and which contains genetic material or protein resulting from the modification. A list of products considered by the ACNFP is included in a separate technical Note A, which is available on request.

12. Some GM foods that have been developed are whole plants or parts of organisms that are eaten raw, such as tomatoes and fresh chicory (used as salad leaves). GM yeasts containing their own enzymes for breaking down sugar to produce more alcohol have been produced for use in brewing beer. GM baking yeasts have also been developed to allow better digestion of sugars obtained from the starch in flour to give a better texture. These yeasts are not yet being used commercially.

13. Many crop plants that are used to produce food ingredients, are now being genetically modified, for example soya and maize. Soya beans can be processed to yield many different food ingredients from soya protein and flour, to oil and lecithins used as emulsifiers. Maize can also be processed to yield a variety of ingredients from starch and sugars to oil and flour. Some ingredients derived from crop plants are very highly refined, for example sucrose and vegetable oils, and these refining processes destroy and remove any genetic material and protein that might be present in the food ingredient. The end product that goes into food is therefore not itself modified and cannot be distinguished from that produced by conventional means.

14. Animals that have been genetically modified to produce pharmaceutical products for use in human therapy do not enter the food chain. No GM animals have been approved for food use.

THE MODERN TECHNOLOGY OF GENETIC MODIFICATION IN MORE DETAIL

15. In essence, genetic modification involves the identification of the gene coding for a particular desired characteristic and the moving of that gene from one living thing where it occurs naturally, to another living thing in which the characteristic is required.

Isolation of DNA

16. Using special enzymes, DNA from the donor organism is cut into shorter pieces containing the gene of interest. These pieces are then separated and purified. The desired gene is then removed from these pieces using specific “scissor” enzymes that cut the DNA molecule only in defined places. The structure and function of these individual genes can then be further defined. The desired gene then has to be transferred into the new host cells.

Transfer and modification of DNA

17. All cells are surrounded by a membrane that cannot be penetrated by large molecules, so it is necessary to have a mechanism for introducing new genetic material into the host cells. In order to ensure that the new gene is incorporated into a cell nucleus as efficiently as possible, a carrier system, or vector is normally used. A typical vector is made up of a circular piece of DNA from a bacterium or virus, which is cut using similar enzymes to those above, in such a way that the new gene can be slotted in.

Multiplication of the desired gene and insertion into the host cell

18. The vector containing the desired gene is then multiplied, normally in bacterial cells, to produce large numbers of the modified gene vector. Consequently the DNA that is inserted is not the original DNA obtained from the donor but a copy of that gene.

19. The plant cells are then transformed by the insertion of vector DNA into the nucleus of the host cell, either using biolistic guns¹ or through the use of a bacterium called *Agrobacterium tumefaciens*, which occurs naturally in soil. A disabled version of this organism can be used as a carrier for DNA but it is unable to survive outside the laboratory. For the insertion to work, the vector must contain promoter genes or 'switches' that allow the DNA to reproduce within bacterial cells. Protoplasts, which are cells without their cell walls, can also be used in genetic modification as a means of fusing cells from different cell types that would not normally combine.

Selectable marker genes

20. The process of getting cells to take up the new DNA is still relatively inefficient and only a small number of cells successfully incorporate the new gene. For this reason, a marker gene is often included in the vector as a way of selecting only those cells that do contain the new DNA. Different marker genes are required for the bacterial multiplication stage and for the plant cell transformation stage. One type of marker gene used at the bacterial stage codes for antibiotic resistance, so that cells which contain the new DNA will not die if grown in the presence of the antibiotic. Other types of marker genes, such as herbicide tolerance, can also be used in some situations.

DNA sequences necessary to control gene expression

21. In order for the desired gene to work in the final host, it is also necessary to incorporate short DNA sequences called promoters, which allow the gene to be switched on. Genes inserted into GM plants need specific promoters to allow the gene to function in the plant. They may also be linked to the bacterial switches which were necessary for the gene to be multiplied in the intermediate bacterial host. These can be removed before introduction into the host plant.

Selection and subsequent propagation

22. Finally, the modified host cells are analysed to confirm that only the desired genes are present. The modified plant or bacteria has to be further selected and rigorously tested before it can be used in food production. For example GM plants will need to be grown over many generations to demonstrate that the genetic modification is stable and that the plant performs in the way expected. The modified variety is then typically crossed with important commercial varieties to introduce the desired characteristic into the varieties used in agriculture. The whole process can take many years to reach this stage. Plants now coming through for approval may have started in the laboratory 10 or 12 years ago.

Other types of genetic modification

23. Genetic modification of food plants or bacteria does not always involve the insertion of genes from unrelated species. Some genetic modifications of crop plants involve the 'switching off' of certain genes, for example those involved in the softening of fruits. In these cases the fruit ripens normally, but does not soften, so

¹ These use high velocity micro-particles or gold or tungsten that are coated with DNA and fired into the cells.

that handling damage and losses are reduced. This 'switching off' may be achieved by the insertion of a copy of the softening gene in the reverse position or by inserting only a part of the normal gene. In both cases, this interferes with the way the cell expresses the normal gene and as a result the protein products from the switched off gene are not made. This process can also be used to eliminate toxic plant products. This is the type of genetic modification carried out on the tomatoes used to produce paste that is approved for sale in the UK.

24. More recent developments in the genetic modification of plants are beginning to allow the expression of the gene to be targeted to only certain parts of the plant, such as the leaves and roots. This is achieved by careful selection of the promoter 'switch'. For example, genes for pest resistance could be expressed only in the parts of the plant susceptible to attack by the pest, and not in the parts of the particular plant used for food.

ASSESSING THE IMPACT OF GM FOODS ON HUMAN HEALTH

25. The purpose of this paper is to address only the safety of foods obtained using genetic modification techniques. Of course, different types of GM food may raise different theoretical concerns and the safety of any particular GM food needs to be considered on a case-by-case basis. Working from first principles, an assessment of the theoretical risks to human health must take account of the nature of the new technology and how it could adversely affect human health. It must also take into account in general terms, the types of human disease processes which can occur and whether they are more likely as a result of these developments.

Theoretical ways in which the genetic modification process could affect human health

26. The theoretical health implications arising from the use of new technologies to manipulate genetic material are as follows:

- i). the inserted gene may itself have adverse effects;
- ii) the inserted gene may code for a protein that is toxic to human beings or produces an allergic reaction;
- iii) the inserted gene may alter the way existing genes in a plant or animal express themselves, which may in turn increase the production of existing toxins or switch on the production of previously silent genes;
- iv) the inserted gene may alter the behaviour of a micro-organism, which is carrying it to make it potentially harmful;
- v) the inserted gene may be transferred from a micro-organism which is carrying it to other micro-organisms, in the human gut or respiratory tract or to animals or humans;

- vi) the consumption of a GM micro-organism may alter the balance of existing micro-organisms in the human gut.

Likelihood of such events affecting human health

27. People are constantly exposed to foreign DNA from the food they eat and from micro-organisms in the environment and those living on their skin and in their digestive and respiratory tracts. DNA itself is not a toxic chemical and consumption of this chemical does not, therefore, have direct toxic effects. In addition, genetic modification results in the transfer of only single genes or small groups of genes, which are well characterised and whose function is understood. Plants typically contain 20-40,000 genes, and the function of the majority of these genes is not yet understood. Traditional plant breeding increases human exposure to some of the products of these genes in a random way that does not first involve their isolation and definition. The random nature of conventional plant breeding has produced potentially harmful products on a number of occasions (see later – paragraph 33).

28. Experiments have shown how difficult it is to introduce genes into human cells. For example, attempts to introduce genes into human cells in the body to replace defective genes, such as those leading to cystic fibrosis, have met with very limited success, even when conditions for transfer are optimised. This would tend to support the view that DNA from GM foods is unlikely to enter human cells.

29. The human intestinal tract is an efficient digestive system and DNA is rapidly broken down under normal conditions into pieces too small to be functional. Thus intact foreign DNA is not thought to be available for transfer into human cells although there is a remote possibility that DNA fragments may be taken up by bacteria in the gut. There is some recent evidence from one group of researchers² to show possible DNA uptake. Under certain conditions, direct feeding of free DNA (obtained from bacteriophages)³ to experimental mice did result in some pieces of this DNA being taken up into cells in the mouse intestine and into other tissues. This has so far not been reported for other DNA sources such as foods and the significance is unclear.

30. There is evidence to support exchange of genes between bacteria in the environment either by direct transformation⁴ or via natural vectors such as plasmids⁵. There is also evidence to support the transfer of free DNA (for example, in soil as a result of the breakdown of plant material) into bacteria in the environment and some recent evidence⁶ has shown the transfer of a marker gene used in genetically modified sugar beet into other plants. However, for this transfer to occur, the free

² Doefler and co-workers in Cologne – a) *Molecular and General Genetics*, 1994, 242(5), p495-504; b) *Molecular and General Genetics*, 1998, 259(6), p569-576; c) *Proceeding of the National Academy of the USA*, 1197, 94(3), p961-966 and d) *Trends in Biotechnology*, 1997, 15(8), p297-301.

³ Bacteriophages are viruses that infect bacteria.

⁴ Transformation is the permanent genetic change made to a cell following the incorporation of new DNA. Some bacterial species can take up DNA from both similar and completely different types of bacteria.

⁵ Plasmids are pieces of DNA that exist outside the cell nucleus.

⁶ Bailey and co-workers, *Molecular Ecology*, 1995, 4 p755-763; Tebbe and co-workers, *Bioengineering*, 1994, 10, p14-28, 21; and Troxler and co-workers, *Applied and Environmental Microbiology*, 1997, 63 p510-613.

DNA has to be relatively stable and persistent. In addition, the recipient bacterium needs to be able to take up the DNA, which then has to be integrated into its own DNA and expressed. For this transfer to have any possible health implications, this integration would need to result in a new form of the bacteria that is stable and that can survive in the environment. The success of DNA transfer and of survival of the recipient bacteria is very dependent on environmental conditions such as temperature, pH and any selection pressures.

31. There are many natural factors that reduce the chances of successful gene transfer, including breakdown of free DNA, the fragmentation of any foreign DNA that enters cells by protective enzymes and host immune defence systems that recognise and destroy invading bacteria.

32. Non-GM micro-organisms have a history of use in agriculture in pathogen control and as a means of increasing nitrogen fixation, without any apparent adverse human health consequences for people. Data from field releases of GM micro-organisms⁷ have not shown any evidence of transfer of selective marker genes from modified bacteria, in which the gene construct was inserted in a stable way, to bacteria in the environment. However, there is evidence to support transfer of DNA from plasmids under laboratory conditions. Studies⁸ of the rate of transfer of inserted marker genes from GM plants into soil micro-organisms has shown that this only happens with a frequency of less than 1×10^{-13} (one in ten million million) under optimised laboratory conditions. The frequencies are less than 1×10^{-16} (one in a ten thousand million million) in field conditions.

Comparable concerns from non-GM foods

33. Some of the issues raised in connection with GM foods are equally applicable to foods produced by conventional means, and there are a number of examples of health concerns arising from traditional plant breeding. These include the Lenape potato (increased solanine levels), vegetable squashes (increased levels of cucurbitin) and celery (increased levels of psoralens). These were not detected until the product was close to release onto the market as none of these developments were required to be subjected to a safety assessment.

POSSIBLE HEALTH OUTCOMES

Communicable disease

34. Any consideration of the impact on communicable diseases must take account of:

- the likelihood of organisms producing more serious effects than they would have previously,
- the emergence of organisms which are more resistant to antibiotics, and
- the creation of new infective agents.

⁷ Bailey and co-workers, *Molecular Ecology*, 1995, 4, p755-763; Tebbe and co-workers, *Bioengineering*, 1994, 10, p22-26; and Troxler and co-workers, *Applied and Environmental Microbiology*, 1997, 63, p213-219.

⁸ Nielsen and co-workers, *Theoretical and Applied Genetics*, 1997, p815-821.

35. Existing plant pathogens, such as viruses, normally only infect a limited number of plants and the metabolic processes in plants are typically very different to those in animals. This reduces the likelihood that such pathogens could 'jump' from one species to another.

36. Bacterial pathogens have a specialised lifestyle and they need to possess many properties to allow them to invade a host and to reproduce there. The safety evaluation of any GM micro-organism that would be consumed in a live form (for example in a yoghurt culture) includes a detailed evaluation of its ability to cause human infection. If the GM micro-organism was to be used to produce food ingredients, such as enzymes, or defined chemicals, the safety evaluation would include evidence to show that there was no DNA or novel protein that might have health implications in the final food product. There is a theoretical possibility that a novel strand of DNA could be generated in GM plants from promoters derived from plant viruses, such as the cauliflower mosaic virus and that such a sequence could then transform a pathogen to express a novel virulence factor. However, given the widespread natural occurrence of this virus in many vegetables, it is more likely that pathogens could evolve novel virulence factors more easily by exposure to the native virus.

Antibiotic resistance

37. The possibility that antibiotic resistance genes might be transferred from GM organisms needs particular consideration. Such resistance genes were often used in the early years of the development of the genetic modification technology as 'selective markers'. However, the use of alternative marker systems, or subsequent deletion of the antibiotic resistance gene, is now becoming more common. Clearly if a GM micro-organism was to be eaten in a live form, it would be unacceptable for it to contain an antibiotic resistance gene. However, the GM micro-organism could be used simply to produce a food ingredient (such as an enzyme). In such a case, the main consideration would be the level of DNA present in the final food ingredient. It would also be important to consider whether that DNA was still functional and was likely to transfer and become active in gut micro-organisms.

38. Several GM plant varieties contain the marker that codes for resistance to the antibiotic kanamycin linked with a plant promoter. This marker system is used to select those plants that have been successfully modified. Such genes would not confer additional kanamycin resistance on bacteria because they are not linked to a bacterial promoter. However, in some crops submitted for approval, an ampicillin resistance gene linked to a bacterial promoter was used. When the Advisory Committee on Novel Foods and Processes (ACNFP) assessed such crops, it did not recommend their approval because of the small risk of transfer of resistance to an important clinical antibiotic.

39. It is considered that transfer of complete antibiotic resistance marker genes from plant material into bacteria present in the human gut in a functional form is very unlikely, but it cannot be ruled out. This needs to be considered in the context of

other causes of the development of antibiotic resistance, such as was recognised by the House of Lords Select Committee on Antimicrobial Agents.

40. Antibiotic marker genes serve no useful purpose in the final modified plant. Indeed, it is now possible to remove such a marker after the initial multiplication step in bacteria but before the novel DNA is introduced into the host plant. Therefore, the ACNFP recommends removal of such intermediary marker genes after the initial modification step as 'best practice' and we support this.

Non-communicable disease, including chronic disease and foetal abnormalities

41. Many diseases are not caused by infections and are often referred to as chronic disease. Most forms of cancer fall into this category, as do diseases like diabetes mellitus, heart disease and arthritis. A proper health assessment of GM foods must examine any likelihood of the incidence of these diseases being increased.

42. Many chronic diseases have a genetic component - that is they relate to the genetic make-up of an individual- although usually other factors are also involved, including diet, environmental exposure to chemicals and/or radiation and lifestyle factors. It is unlikely that the genetic component could be influenced by consumption of GM foods as the evidence suggests that DNA from foods is not likely to be incorporated into human cells.

43. Some conventional plants produce chemicals as a defence mechanism against attack by insects or as protection against adverse conditions, such as the glycoalkaloids produced in potatoes. Some of these naturally occurring chemicals may be harmful to humans and can cause cancer and foetal abnormalities in animals. It is for this reason that those involved in the preparation of food must take care to avoid green potatoes and to boil red kidney beans. The history of any host plant that is being genetically modified needs to be evaluated. This would include considering whether the production of toxins known to be associated with the plant or its close relatives, was increased. Of course traditional plant breeding could also result in changes in toxin-producing potential, and this needs to be considered in both types of plant breeding.

44. The incidence of some chronic diseases may be influenced by nutritional factors and this issue is dealt with in the section which follows.

Nutritional imbalance effects

45. The incidence of many human diseases is dependent on a number of risk factors including dietary variables such as fat intake and antioxidant levels in food. Genetic modification of an organism used for food may result in the composition of the final food product being different to that of the conventional food it would replace. This may be the intended consequence of the modification (for example altered starch composition in potatoes, altered levels of beneficial nutrients such as antioxidants in fruit and vegetables, or altered levels of fatty acids in oils from oilseed crops), or it may be unintended. The safety evaluation of all GM foods includes a consideration of any possible nutritional effects of the novel food. The cumulative

effect of individually insignificant changes in the composition of the overall diet needs to be considered, especially for those groups of the population such as infants whose diets are derived from a limited number of food items.

Altered immune response

46. Some chemicals can alter immune responsiveness, either increasing it, leading to allergy, or depressing it. This possibility needs to be considered in the assessment of any new GM food. The insertion of genes that code for novel proteins not normally present in traditional food products may result in increased allergic reactions in some consumers. The allergenic potential of the modified food product is evaluated as part of the overall food safety assessment, particularly if either the source of the inserted genes, or the host are known to cause allergy. This includes comparing the structure of the gene products with the known allergens. It is also important to consider how functional the protein gene product would be in the food as consumed (after processing and/or cooking), the level at which it might be present and the likelihood that it would resist the digestive process in the gut. Assessment of potential allergy is complicated by the lack of suitable animal models that can be used on a routine basis in safety evaluations, although research is underway to find mechanisms to identify proteins that are likely to cause an allergic reaction.

47. It has been suggested from the results of the work by Dr Pusztai on GM potatoes that consumption of genetically modified food may result in depression of the immune system. The mechanisms by which this could occur are unclear. This work has been reviewed by the Royal Society, who concluded, on the basis of the information made available to them, that the work appeared to be flawed in many aspects of the design, execution and analysis and that no conclusions should be drawn from it. They found no convincing evidence of adverse effects from the GM potatoes studied. They also concluded that it would be unjustifiable to draw any general conclusions about the safety of GM foods in general from the results of studies, however well conducted, on one particular product modified by the insertion of one particular gene by one particular method - see also paragraph 56 below.

Indirect effects

48. This paper has considered possible direct effects on health resulting from consumption of GM foods. It is possible that indirect effects on human health may arise from effects of GM organisms on the wider environment, and such an assessment is made as part of the evaluation of the release of GMOs to the environment under the Deliberate Release Directive 90/220/EEC. In addition the possible consequences for human health of the consumption of GM feed products by farm animals is subject to the same rigorous assessment procedures as GM foods.

49. The genetic modification of plants to introduce herbicide resistance or insect tolerance traits is intended to reduce the overall amounts of herbicidal and insecticidal chemicals sprayed onto the plants. This may result in final food products with lower concentrations of chemical residues.

50. A detailed discussion of the wider environmental issues is outside the scope of this paper.

Particular examples of health concerns

51. Some specific health worries have been raised in relation to the use of genetic technology in food production and we comment on these below.

Tryptophan

52. It has been argued that genetic modification was responsible for several deaths in the USA. Contaminated tryptophan, a food supplement was implicated in the human disease known as Eosinophilia Myalgia Syndrome (EMS). The particular tryptophan involved was produced by fermentation involving a GM bacterium. The contamination was linked to 37 deaths in the late 1980s in the US. Following an in-depth investigation, the US Food and Drugs Administration could not find any evidence to suggest that the contaminant was produced as a direct consequence of the genetic modification process.

53. An investigation reported in the New England Journal of Medicine in 1990 identified an association between the EMS cases and a reduced level of carbon in a purification step in the production of the supplement involved, in addition to the genetic change in the bacterium strain. In a 1992 report the US Department of Health and Human Services noted that 3-5% of the EMS cases had not been definitively linked to the supplement involved, and at least eight cases were linked with tryptophan obtained from ordinary plant sources. The report also noted that cases of EMS were occurring prior to the 1989-90 epidemic.

54. Recent United States Food and Drug Administration reports have found the impurity linked with the development of EMS in a number of both synthetic and natural versions of the tryptophan on sale as supplements for insomnia. It is therefore inappropriate to conclude that the cases of EMS were only linked to tryptophan produced by GM bacteria.

55. This case illustrates the importance of strict quality control monitoring for all food products. Such information is an essential part of the safety assessment procedure for GM foods.

Work by Dr Pusztai on GM potatoes

56. Work was undertaken at the Rowett Institute by Dr Pusztai, in which potatoes were genetically modified to express an insecticidal lectin protein. The results have been widely reported to suggest that the process of genetic modification itself may be harmful for health. The results of this work have been reviewed by the Royal Society, who concluded, on the basis of the information made available to them, that the work appeared to be flawed in many aspects of the design, execution and analysis and that no conclusions should be drawn from it. They found no convincing evidence of adverse effects from the GM potatoes studied. They also concluded that it would be unjustifiable to draw any general conclusions about the safety of GM foods in general from the results of studies, however well conducted, on one

particular product modified by the insertion of one particular gene by one particular method. It should be noted that these potatoes were not intended for marketing and had not been submitted for marketing approval. If they had been submitted, they would have been subject to a detailed safety assessment concentrating on the safety implications of the expression of the lectin gene, as some lectins are well known to exert toxic effects in animals and humans.

Ladybirds

57. Some work has been reported which indicates adverse effects in ladybirds eating aphids that have been colonising potatoes genetically modified to express an insecticidal lectin protein. The evidence has been considered by the Advisory Committee on Releases to the Environment (ACRE), which concluded that the findings are consistent with the known toxic properties of the lectin. This work underlines the need to conduct thorough testing of GM crops for indirect effects on non-target organisms.

Milk from cows treated with BST

58. Bovine somatotrophin (BST) is a hormone which is naturally produced by all cows. It stimulates milk production and minute quantities are present in all cows' milk, particularly in high yielding dairy cows. BST made using genetic modification is widely used in the USA to increase milk production. In the UK, BST falls within the definition of a medicinal product and it cannot be marketed here without a marketing authorisation. Following evaluation by an expert committee in Europe, the EC has accepted that milk from treated cows may contain increased amounts of a growth factor, which may be associated with some adverse effects in humans. For this reason and because of animal welfare issues, there is a moratorium on the marketing and use of the product in the Community which expires at the end of December 1999. This is to allow for practical tests to be carried out to obtain further scientific data needed to enable the Council of Ministers to make a final decision. The UK Veterinary Products Committee has set up a working group to advise on the safety of BST for the target animal and for humans consuming milk from treated animals. This group is due to report this summer.

CURRENT SAFETY ASSESSMENT PROCEDURES

Legislation

59. The approval of GM foods is regulated by EC legislation. Accordingly, Member States cannot introduce their own requirements in this area without agreement of the other countries of the Commission, who are advised by the EC Scientific Committee for Food.

Novel Foods Regulation

60. There is now in place a comprehensive EU wide regulatory framework controlling all aspects of GM crops in Europe from seeds to final food products. The main food related legislation is the EC Regulation on Novel Foods and Novel Food

Ingredients (258/97) which came into effect on 15 May 1997. This Regulation introduced a statutory pre-market clearance system for all novel foods, including those produced using genetic modification, and it is binding on all Member States. The Regulation is accompanied by Commission Guidelines on the data required to support an application and on how applications should be assessed. These guidelines closely resemble the approach to the safety assessment of novel foods that was developed in the UK over a number of years. They also follow internationally accepted best practice which has evolved over the last 10 years. Under this regulation, the safety of individual GM foods is assessed by all Member States and any differences of scientific opinion are resolved by reference to a number of scientific committees of the European Commission.

Advisory Committee on Novel Foods and Processes (ACNFP)

61. Ministers are advised on all novel foods, including those produced using genetic modification, by an independent committee of experts, the ACNFP. This committee carries out safety assessments of individual novel foods as part of the pre-market approval scheme controlled by the EC Novel Food and Novel Food Ingredient Regulation. In carrying out such assessments, the ACNFP can seek specialist advice from other Government advisory committees, such as the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment or the Committee on Medical Aspects of Food and Nutrition Policy. ACNFP can also seek advice from the Food Advisory Committee on the labelling of GM foods and on any general issues arising from individual applications. The ACNFP holds joint meetings with these other committees and the wider scientific community to discuss more general technical issues, as the need arises. In all, over 60 practising scientists, the vast majority of which are leaders in their fields with international reputations, are involved in assessing novel foods in the UK.

62. The ACNFP itself consists of 14 members with expertise in areas such as genetic modification, toxicology, nutrition, microbiology, biotechnology and food processing, as well as an ethicist and a consumer representative. Its job is not only to assess individual applications in as rigorous a manner as possible, but to keep up to date with the emerging science in this rapidly growing area and to advise on changes to the assessment procedure in the light of this.

63. All the agendas and minutes of the committee meetings are published on the Internet. The individual assessment reports produced by ACNFP are also published, as well as being brought together in an Annual Report. Companies making applications are strongly encouraged to deposit as much of the supporting data as possible in the British Library where it can be inspected by anyone with an interest.

Food Safety Act

64. This Act, which was introduced in 1990, continues the basic requirement that has been embodied in food law for almost 150 years that no food should be injurious to health.

Products considered

65. A list of those products which have been considered in the UK is contained in a technical annex to this paper, which can be obtained on request. The ACNFP takes a cautious approach to all assessments and no approval is recommended unless it is completely satisfied that all aspects of safety have been thoroughly examined. If the Committee is not fully satisfied of the safety of the food in question it does not recommend approval. Only three foods, GM soya, maize and tomato paste, have so far entered the UK food supply.

Animal feedingstuffs

66. There is a theoretical possibility that modified genes in GM feed might cross the gut and enter the cells of animals used to obtain human foods and this was considered in paragraphs 28 and 29. The majority of feed materials are processed by-products and we are not aware of any evidence that modified genes are present in milk, eggs or other animal products. It is likely that some GM material is being fed to animals, although this cannot be quantified in the absence of crop segregation and specific labelling requirements. The Government is setting up an Advisory Committee on Animal Feedingstuffs, which will consider human and animal health aspects of animal feeds, including those produced using GM. Decisions on the proper labelling of GM animal feed material must be taken in Europe.

Approach to the assessment of GM foods in comparison with the evaluation of medicines

67. It has been suggested that the safety of novel and GM foods should be assessed in a similar way to that used for pharmaceutical products. The ACNFP has recently considered this issue and has advised that long term feeding studies should be carried out where it is relevant and appropriate to do so. However each case needs to be considered on its merits. Complicating factors in the design and interpretation of long term studies when applied to foods, as opposed to pure chemicals, mean that it is unlikely that they would give rise to meaningful information in all cases.

68. Pharmaceutical products are generally well characterised materials of known purity, of no nutritional value and human exposure levels are normally low. It is relatively straightforward therefore to feed such compounds to animals at a range of doses, some orders of magnitude greater than the expected human exposure levels in order to identify any potential adverse effects of importance to humans. In this way it is possible, in most cases, to determine levels of exposure at which adverse effects are not present, and so set safe upper limits by the application of appropriate safety factors.

69. In contrast, foods are complex mixtures of compounds characterised by wide variation in composition and nutritional value. Due to their bulk and effect on appetite they can only be fed to animals at low multiples of the amounts that might be present in the human diet. In addition it is important when conducting animal studies on foods to consider the nutritional value and balance of the diets used to try to avoid the induction of adverse effects which are not due directly to the material itself. Picking up any potential adverse effects and relating these conclusively to an individual characteristic of the food can therefore be extremely difficult.

70. Very few foods consumed today have been subject to any toxicological studies. The safety assessment of the many thousands of food products launched each year in the UK is generally based on the assumption that since the individual ingredients already have an extensive history of consumption a new combination of such ingredients will be equally safe. Nevertheless many existing foods would be likely to show adverse effects if they could be fed at high enough doses. Given the practical difficulties of conventional animal toxicological studies in the assessment of food safety an alternative approach using the concept of substantial equivalence was devised where the safety assessment is focused on any differences between the GM food and its non-GM counterpart.

How safety is assessed using a comparative approach

71. The safety of GM foods is assessed in comparison with the foods that they will replace. This concept of **substantial equivalence** developed by the World Health Organisation and the Organisation for Economic Co-operation and Development is used extensively as a tool in the process of the assessment of the safety of GM foods by expert assessment bodies world-wide. The fact that a GM food may be substantially equivalent to a conventional one does not, however, mean that it is 'safe'. Nor does it remove the need for a thorough assessment to be carried out to ensure that this is so before it can be allowed on to the market.

72. In this assessment method, the GM food is compared to its conventional counterpart and consideration is given to both the intentional effects of the modification and also to any possible unintended secondary effects. This comparison involves the assessment of a wide range of information. This includes agronomic data derived over a number of generations (such as crop height, yield, flowering pattern, disease resistance and climatic tolerance) and detailed compositional information on nutrients (proteins, fats, carbohydrates, vitamins and minerals) and possible toxicants in both the plant and any derived food product. This comparison can have three possible conclusions:

- the GM food or food ingredient is substantially equivalent to the conventional counterpart in all agronomic, compositional and toxicological respects;
- the GM food or food ingredient is substantially equivalent to the conventional counterpart except for a few clearly defined differences; or
- the GM food or food ingredient is not substantially equivalent because the differences cannot be defined or because no counterpart exists.

73. In the first and second categories above, a safety assessment is carried out with particular attention being focused on any differences between the GM food or food ingredient and its conventional counterpart. Where a food is not substantially equivalent, it does not mean that the food is unsafe but extensive data would need to be provided to demonstrate its safety. We have produced a separate technical note (note B which is available on request) describing the history of how the current UK and European safety assessment procedures were developed.

Information requirements for safety evaluations

74. As a starting point, the safety assessment of a GM food involves a careful assessment of the following information:-

- the amounts of the GM food that people are likely to consume, including both average and extreme consumption;
- a detailed description of what the food is and how it is produced;
- a history of any possible adverse health effects linked to the organism being modified;
- a detailed description of the genetic modification process;
- an evaluation of any possible nutritional effects of the modified food;
- an evaluation of any toxicological effects of the modified food;
- an evaluation of any adverse microbiological effects of the modified food;
- an evaluation of any data on people eating the modified foods under controlled conditions.

75. The detailed issues considered as part of the evaluation of any GM food are described in a separate technical note (note B which is available on request).

International perspective

76. The safety considerations for GM food have been considered in many other countries and by international organisations such as the World Health Organisation. Many GM foods are now being marketed in other countries such as the USA and Canada, following approval by their regulatory authorities. However these products still need to be assessed for safety under the EU regulatory framework before they can be marketed in Europe. After such approvals have been given, the World Trade Organisation Sanitary and Phytosanitary Agreement rules prevent countries from taking action to restrict the import of such products into their markets unless evidence of harm subsequently comes to light.

77. The US and Canadian systems (see the separate technical note C which is available on request) place responsibility for ensuring safety on the GM food producer and such foods do not therefore require prior assessment by the regulatory authorities before being allowed onto the market, as is the case in the EC. In this regard the EC system may be considered to take a more precautionary approach to the approval of these materials. In July 1998 the US Department of Agriculture and the Canadian Food Inspection Agency reached a bilateral agreement on the data required for the molecular genetic characterisation of GM plants. This agreement was seen as a first step towards the harmonisation of such data requirements.

Population health surveillance

78. Although there is a rigorous pre-market safety assessment of GM foods, no systematic population surveillance system currently exists to detect any effects on health. This is a weakness in the present system. Surveillance of health at a population level is essential and there are existing databases covering key health outcomes, such as cancer, foetal abnormality, and mortality which could be used in this respect.

79. An ACNFP Working Group has been considering the feasibility of setting up a population surveillance system to provide additional reassurance on the long term safety of those GM foods that have been approved for marketing. This could involve case-by-case studies of individual GM foods or more general epidemiological studies to evaluate the unanticipated consequences for health (adverse and beneficial) of GM foods more generally. The Medical Research Council is also setting up an expert group to consider the feasibility of large scale epidemiological studies to evaluate the potential health effects (both beneficial and deleterious) of GM foods more widely. We await their conclusions but see merit in considering establishing a new unit to act as a surveillance at population level of any health impact of genetically modified and other types of novel foods. The unit would act as an early warning of serious problems and could also continuously monitor the world's health literature and advise on the significance of any new research when it becomes available.

CURRENT AND FUTURE RESEARCH ON GENETICALLY MODIFIED FOOD ISSUES

80. An extensive research programme exists to ensure that the assessment system is kept at the forefront of scientific advances.

81. Government has had a sizeable and expanding programme of research on the safety of novel foods for some years now (more than £1 million was spent on this in financial year 1998/99). The objective of this programme is to provide information needed to safeguard the consumer from any risks associated with the consumption of novel foods. Research projects to date have fallen into the broad areas of analysis; labelling and risk evaluation and have covered the genetic stability of crop and model plant species after transformation, gene transfer and the implications for safety of novel gene expression.

Projects include work on:

- Methods to detect GMOs in processed and unprocessed foods;
- Development of databases on genes that have been introduced by genetic modification of crops intended for food use;
- Development of methods to predict the allergenic potential of genetically modified foods and novel protein products;
- Investigation of the transfer of genetic material to gut microflora from ingested GM micro-organisms;
- Investigation of Agrobacterium as a vehicle of gene escape;
- Investigation of the stability of expression and inheritance of transgenes; and
- Investigation of the effect of background genotype on transgene expression.

82. Government also funds programmes studying possible risks to the environment from the release of GMOs, including research on the impact of the introduction of GM oilseed rape on agriculture; potential effects of changes of herbicide usage arising from planting of tolerant GM plants; the role of bees in pollen transport between sites and the impact of transgene movement by pollen to weed species. Research is also underway to assess risks from the release of GMOs and to design

proper controls over such releases. This includes projects looking at environmental impact of insect and disease resistance in GM plants and the impact of multiple tolerance in GM plants.

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

83. We have considered the processes used in genetic modification in relation to events occurring in nature and in conventional plant breeding and we conclude that there is no current evidence to suggest that the process of genetic modification is inherently harmful. Many of the issues raised by foods produced using genetic modification are equally applicable to foods produced by conventional means. We are reassured by the precautionary nature and rigour of the current procedures used to assess the safety of individual GM foods. Nevertheless, nothing can be absolutely certain in a field of rapid scientific and technological development. Genetic modification is a young science and there is a need to keep a close watch on developments and to continue to fund research to improve scientific understanding in this area. We welcome the recent moves to improve the openness of the regulatory procedures to public scrutiny and would encourage further such moves to help to inform public debate on the issues relating to the health implications of GM foods.

Recommendations

84. We make the following recommendations:-

Tracking research and acting on new evidence

Government advisory bodies should continue to closely monitor developments in scientific knowledge and regulation on an international basis and provide advice on any fresh action which they consider necessary.

Promoting high standards of regulation

The United Kingdom's current system of regulation of GM food technology and other novel foods is rigorous. We propose that the Government should offer its expertise and use its influence to promote high standards of regulation internationally.

The need for a continuing research strategy

Government should continue to fund research to improve scientific understanding and to fill gaps in current knowledge. We propose that the Government should invite the Medical Research Council and other major research bodies to participate in the further development of this research strategy. We propose that before any new research is acted upon by Government, it must have been through the standard peer review process to ensure that it has scientific credibility. Government's own response to new data should be made in line with the *Guidelines on the Use of*

Scientific Advice in Policy Making to allow the full scientific merits of new research to be assessed.

Instituting population health surveillance

The development of robust population health surveillance in relation to consumption of GM and other novel foods is essential to ensure that Government is able to respond rapidly should any unexpected effects occur. The Advisory Committee on Novel Foods and Processes and the Medical Research Council are already discussing how this might be done. As part of this, consideration also needs to be given to the establishment of a national surveillance unit to monitor population health aspects of genetically modified and other types of novel foods. Surveillance could be used to examine trends over time to detect any early changes in the incidence of adverse health outcomes, whilst recognising the difficulties in establishing causal relationships.

Antibiotic resistance marker genes

The use of alternatives to antibiotic resistance genes as part of the GM process is already stated good practice by the Advisory Committee on Novel Foods and Processes. We recommend that those who are developing foods using genetic modification should be encouraged to phase out the use of antibiotic resistance marker genes as soon as is feasible.

Suggested further reading

Regulation 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Official Journal of the European Communities No L 43/1, dated 14/2/97.

EC Scientific Committee for Food, opinions on the Assessment of Novel Foods, Official Journal of the European Communities, No L 253, dated 16/9/97.

Royal Society Statement on Genetically Modified plants for food use. 3 September 1998.

House of Lord Select Committee on Science and Technology (Sub Committee 1) Inquiry into Resistance to Antimicrobial Agents. April 1998.

Advisory Committee on Novel Foods and Processes. Guidelines on the Assessment of Novel Foods and Processes. Department of Health. Report on Health and Social Subjects 38. 1991.

Advisory committee on Novel foods and Processes. Report on the Use of Antibiotic resistance markers in Genetically Modified Food Organisms. July 1994.

Advisory Committee on Novel Foods and Processes. Report of the use of antibiotic resistance marker in genetically modified plants for human food. Clarification of Principles for decision Making. July 1996

Advisory Committee on Novel Foods and Processes. Paper on the toxicological assessment of novel foods. 1998 (Available from the ACNFP Website on <http://www.maff.gov.uk/food/novel/acnfp.htm>)

Royal Society review of data on possible toxicity of GM potatoes. 18 May 1999

Joint Food and Agriculture/World Health Organisation Consultation. Strategies for Assessing the Safety of Foods produced by Biotechnology. 1991.

Report of the Committee on the Ethics of Genetic Modification and Food Use. Ministry of Agriculture, Fisheries and Food. London: HMSO 1993.

The Use of Scientific Advice in Policy Making. Published by Department of Trade and Industry. March 1997.

Genetically Modified Foods: Facts, Worries, Policies and Public Confidence. Published by Department of Trade and Industry February 1999.

House of Commons Science and Technology Committee. Scientific Advisory System: Genetically Modified Foods. HMSO 18 May 1999.

TECHNICAL ANNEXES

Annex A : List of GM foods considered in the UK

A. Products receiving clearance

Date	Product
March 1990	Baker's yeast
January 1991	Chymosin (an enzyme) from <i>E coli</i> *
May 1991	Chymosin (an enzyme) from <i>Aspergillus niger var awamori</i> *
March 1992	Chymosin (an enzyme) from <i>K lactis</i> *
February 1994	Amylolytic yeast for use in brewing
February 1995	Herbicide (glyphosate) tolerant soya beans (Monsanto) *
February 1995	Oil from oilseed rape – hybrid breeding system (Plant Genetic Systems)
February 1995	Tomato paste (Zeneca) *
May 1995	Oil from herbicide (glufosinate) tolerant oilseed rape (AgrEvo)
September 1995	Oil from oilseed rape – hybrid breeding system (Plant Genetics Systems)
December 1995	Hemicellulase (an enzyme) from <i>Aspergillus niger</i> and <i>Bacillus subtilis</i> (advice to the Food Advisory Committee on the genetic modification aspects only)

February 1996	Flavr Savr tomato (Calgene)
February 1996	Tomato paste extension to 1995 clearance (Zeneca) *
May 1996	Processed food products from insect resistant (Bt) maize (Ciba Geigy, now Novartis) *
January 1997	Riboflavin from <i>B subtilis</i> (Hoffman-La Roche)
February 1997	Processed food products from herbicide (glufosinate ammonium) tolerant maize (AgrEvo)
February 1997	Processed food products from three insect resistant (Bt) maize (Monsanto, Pioneer Hi-Bred International and Northrup King)
January 1997	Oil from herbicide (bromoxynil) tolerant cottonseed (Calgene)
January 1997	Hemicellulase (an enzyme) from <i>Aspergillus oryzae</i> (advice to the Food Advisory Committee on the genetic modification aspects only)

* Products known to be on sale in UK

B. Other products considered

A number of other applications involving foods obtained from genetically modified sources have been assessed in the UK but have not been approved due to lack of adequate information:

1. Prior to introduction of the Novel Food Regulation

- Oilseed rape with high lauric acid content
- Insect protected (Bt) maize

2. After introduction of the Novel Food regulation

- Insect protected (Bt) cottonseed (application for opinion on substantial equivalence)
- Herbicide (glyphosate) tolerant cottonseed (application for opinion on substantial equivalence)
- Chicory (*Radicchio rosso* and green hearted chicory) lines for use in a hybrid breeding system
- Insect protected potato (application for opinion on substantial equivalence rejected as not appropriate route for evaluation)
- Insect protected maize (application for opinion on substantial equivalence rejected as not appropriate route for evaluation).

Annex B

History of UK ACNFP guidelines for the safety assessment of novel foods and development of guidance from the European Commission

1. The UK has had a system for assessing the safety of all novel foods for a number of years and the first novel food, mycoprotein, was cleared in 1983. The Government receives advice in this area from the Advisory Committee on Novel Foods and Processes (ACNFP), which was reconstituted in 1988 from the previous Advisory Committee on Irradiated and Novel Foods. ACNFP has considerable experience in assessing the safety of novel foods, including those produced using genetic modification, having been considering these issues for over 10 years.

Decision Trees

2. There are a wide range of foods and food ingredients encompassed within the term “GM food” and the information needed to support an application for approval of an individual GM food needs to address the specific safety issues relevant to that particular food. For this reason it is not possible to set out a checklist of information that needs to be submitted in all cases. The UK, and Europe as a whole, has developed a series of decision trees that use structured series of questions to identify the information requirements of a particular novel food. The European decision trees form the basis of the guidance which lays down how safety assessments of novel foods should be conducted. This guidance (Official Journal of the European Communities L253 of 16 September 1997), which was developed by the Scientific Committee for Food on behalf of the Commission to accompany the Novel Food Regulation, is followed by all MS to ensure a consistent approach across Europe. These decision trees cover:

- the specification of the novel food;
- the effects of any production processes applied to the novel food;
- the history of the organism used as the source of the novel food;
- the effect of the genetic modification on the properties of the host organism;
- the genetic stability of the modified organism used as the source of the novel food;
- the specificity of expression of the novel genetic material;
- the transfer of the novel genetic material from the modified organism;
- the ability of the modified organism to survive in and colonise the human gut;
- the anticipated intake and extent of use of the novel food;
- information from previous human exposure to the novel food or its source;
- nutritional information;
- microbiological information; and
- toxicological information.

Substantial Equivalence

3. The first steps towards international harmonisation of the food safety assessment of GM foods were taken by the Food and Agriculture Organisation and the World Health Organisation in 1990. They convened an expert consultation on the ‘Assessment of Biotechnology in Food Production and Processing as Related to Food Safety’. This consultation recommended that the safety assessment of foods produced by biotechnology should take into account the molecular, biological and chemical characteristics of the food under assessment. The consultation recognised

the limitations of traditional toxicological test methods when applied to whole foods and recommended that a more structured approach to safety assessment should be developed. One of the key conclusions was that the use of genetic modification techniques **‘does not result in food which is inherently less safe than that produced by conventional means’**.

4. The 1990 consultation identified the comparative principle whereby the food being assessed is compared with one that has an accepted level of safety, as being of considerable importance. In 1991 the OECD expanded upon this comparative principle and formulated the concept of substantial equivalence. The WHO and FAO refined the concept at an expert consultation meeting held in Rome in 1996. In the report of this meeting substantial equivalence was identified as being **‘established by a demonstration that the characteristics assessed for the genetically modified organism, or the specific food product derived therefrom, are equivalent to the same characteristics of the conventional comparator. The levels and variation for characteristics in the genetically modified organism must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of data.’**

5. Before a comparison can be undertaken it is necessary to characterise the GM variety to ensure that the appropriate characteristics are assessed. The 1996 FAO/WHO report identifies a number of pieces of information that will be of use in this respect. In addition to details of the host organism and details of how the host has been modified it is necessary to characterise the food product itself. It is essential to look not only for intentional changes but also to consider any unintentional changes. In characterising the food product, it is important to consider both phenotypic* characteristics and compositional analysis. The type of phenotypic characteristics assessed for a GM plant would include crop morphology, growth, yield and disease resistance. In assessing the composition of the GM product the FAO/WHO report identified the need to consider key nutrients and toxicants of the food in question. The report also commented that ‘analysing a broader spectrum of components is generally unnecessary, but should be considered if there is an indication from other traits that there may be unintended effects of the genetic modification.’

Issues considered during the safety assessment of individual GM foods

6. Animal studies are a major element in the safety assessment of many chemical compounds, such as food additives, pesticides, pharmaceuticals and industrial chemicals. In most cases the test substance is well defined and its purity is known. Such chemicals normally have no nutritional value and human exposure is generally low. It is therefore relatively straightforward to carry out toxicity tests in animals. These use a range of dose levels, including some at several orders of magnitude greater than the expected human exposure levels. In this way, any potential adverse effects of importance to man can be identified. Using such studies, it is usually

* phenotype is the appearance or other characteristic of an organism resulting from the interaction between its genetic make-up and the environment

possible to determine dose levels at which the adverse effect is not seen. Thus it is possible to set safe upper limits by the application of appropriate safety factors.

7. In contrast, foods are complex mixtures of compounds characterised by wide variation in composition and nutritional value. Therefore foods, because of their bulk and effect on appetite as well as on nutritional balance, can only be added to the normal diet of an animal at low multiples of the amounts that might be present in the human diet. Thus, in such circumstances, it can be very difficult to pick up any potential adverse effects or to relate any effect seen to an individual characteristic of the food. The role of animal toxicological studies in the safety assessment of GM foods was recently reconsidered by the ACNFP and their conclusions published on the ACNFP page on the Internet (<http://www.maff.gov.uk/food/novel/acnfp.htm>).

8. There is a remote possibility that levels of a previously unknown toxin, allergen or antinutrient might be elevated as an unintended consequence of the modification and not be detected by the compositional analyses. Modern molecular approaches could be used to enhance the ability to compare the whole genome of the parent organism with that of the GM derivative, to give further reassurance that no unintended effects had occurred as a result of the genetic modification. In the future it may be possible to use genomic, proteomic and/or metabolic profiling approaches to further increase the robustness of the substantial equivalence principle as a safety evaluation tool, but at present such approaches are not sufficiently developed for routine use in this way.

9. The assessment of the safety of a GM food or food ingredient embraces a number of issues:-

i) toxicity of the inserted genes

10. All foods consumed raw or only lightly processed will contain genetic material which is readily digested in the human gastrointestinal tract. The inserted genes, which will comprise only a minute fraction of the total genetic material in the modified organism, will be digested in the same way as the genes already present in the organism. Therefore, it is highly unlikely that consumption of the inserted gene itself would have any implications for health. Nevertheless this issue is carefully considered in the case of each application. Some people have questioned the safety of the promoter obtained from the cauliflower mosaic virus (CaMV). This virus occurs world-wide in temperate regions and is commonly found in commercial crops of cabbage, cauliflower and Brussels sprouts, as well as Chinese cabbage. People have therefore consumed it for very many years. Given the widespread occurrence of this virus, it is more likely that pathogens could develop novel virulence factors through exposure to the native virus, than through exposure to the promoter in a GM crop. The developing science of genomics* may be able in the future to help identify any potential novel virulence factors that might evolve

ii) toxicity of the products of the inserted genes -

* Genomics involves the construction of libraries of DNA sequences which can then be used as a screening method to assist in the isolation of particular gene sequences

11 If a novel protein is present in the derived food products, this can be extracted and its toxicity investigated using conventional toxicity tests. Any novel protein is likely to be digested in the same way as the many conventional proteins already present in that food. Nevertheless, the safety assessment of all GM foods includes an evaluation of the toxicity of any protein products of the inserted genes. Nothing is assumed beforehand or taken for granted.

iii) allergenicity of the products of the inserted genes

12. The safety assessment of GM foods includes a consideration of potential allergenicity. Many foods derived from GM organisms undergo considerable processing before consumption, which might destroy any novel proteins. If intact, novel proteins are present, their allergenic potential needs to be assessed. This includes a consideration of the allergenicity of the host organism, as well as that of any organisms used as sources of the inserted genes, together with that of any taxonomically related species. Foods containing genes from plants known to be associated with serious allergenicity are not allowed onto the market if there is any likelihood that public health will be adversely affected.

13. The case of the genetic modification of soya beans intended for use as animal feed shows the robustness of such evaluation systems. A gene from brazil nuts was inserted into the soya to improve the protein quality of the bean. The safety testing that was conducted identified that the inserted gene was allergenic and thus the plant was never commercialised. In addition, this information helped to identify the particular protein in brazil nuts responsible for its allergenicity. This allergen is now included in the databases known allergens that novel proteins arising from genetic modification can be compared against.

14. Genetic modification could be used to reduce the allergenicity of certain plants and a low allergenic rice is currently being developed. The amino acid structure of the novel protein can be compared with that of known allergens to look for any similarities. If similarities are found, it is important to consider whether the novel protein is able to resist digestion and heat, as most known allergens are not broken down by heat and digestive enzymes. Reliable and predictive tests for potential allergenicity are not available at present and research to develop such tests is currently being carried out. As an additional safeguard, consideration is always given to the need for some form of post market monitoring or surveillance to be carried out as a condition of the approval. Such arrangements were put in place when (non GM) lupin flour was approved to enter the food supply in 1997.

15. It should also be remembered that novel exotic foods being introduced into Europe from elsewhere in the world may represent an allergenic risk, the kiwi fruit being a good example.

iv) transfer of genes encoding antibiotic resistance

16. Antibiotic resistance genes are sometimes used early in the genetic modification process as selective markers. If such genes are present in the final food products, any safety implications that they might raise are thoroughly evaluated. The ACNFP considered this issue in detail in 1994 and 1996. Their conclusions are that GM

micro-organisms consumed in a viable form should not contain antibiotic resistance marker genes. All other GM foods need to be assessed on an individual basis, taking into consideration the likelihood of transfer of the gene, its subsequent maintenance and expression in micro-organisms found in the human gut and the clinical use and importance of the antibiotics for which resistance is encoded. In addition to possible transfer to gut micro-organisms, it is also important to consider the likely levels of exposure and the possibility of transfer into bacteria present in the mouth and in the respiratory tract as a result of exposure via pollen and other airborne sources such as dusts generated by dry milling.

17. It is also known that some ampicillin resistance genes have undergone point mutations, which resulted in extension of the range of antibiotics that could be inactivated by the products of the resistance gene, to include a number of clinically important cephalosporins. If such point mutations occurred in antibiotic resistance genes used as selective markers, which subsequently transferred into gut micro-organisms, this could have implications for the clinical treatment of serious infections including meningococcal meningitis or any other disease. But it does not mean that new strains of meningitis are likely to be created by the use of antibiotic resistance marker genes in GM crops.

18. Using this precautionary approach, the ACNFP has recommended rejection of three applications submitted to it. These cases involved a maize containing an ampicillin resistance marker gene and two GM cottonseeds containing a gene conferring resistance to streptomycin and spectinomycin. It was considered that there was a very small, though finite risk of transfer of resistance to micro-organisms in the intestinal tract of animals fed unprocessed plant material (processing destroys the antibiotic resistance gene), and that this could compromise clinical therapy in man. Other factors such as clinical and veterinary use of antibiotics and their use as growth promoters in animal feed are likely to have a much greater effect on the occurrence of resistance in the wider environment than possible transfer from GM plants. Nevertheless, the ACNFP believes that it is right to be cautious about their use in genetic modification. This was recognised by the recent House of Lords Select Committee on Science and Technology Report on Resistance to Antimicrobial Agents.

v) Nutrition

19. Any nutritional consequences of the consumption of the GM food need to be considered, both in terms of possible changes in the levels of nutrients in the food itself and also in terms of the effects on the overall diet of replacing a conventional food with the GM one. It has been recognised for a long time that whereas each individual change may not be significant on its own, cumulative effects on nutrient intake may be significant. However this is equally applicable to changes in food products arising from conventional plant breeding and a recent joint meeting of ACNFP and the Committee on the Medical Aspects of Nutrition Policy has recommended building on current diet and nutrition data collection systems to monitor this issue.

vi) GM micro-organisms

20. The safety assessment of all GM micro-organisms is conducted using experience and background acquired in the assessment of the safety of non-GM micro-organisms. This assessment takes into account whether or not the final food will contain viable micro-organisms, and includes a full characterisation of the inserted DNA, including the sources from which it was obtained, plus a history of human exposure to the host organism and any associated health effects. Information is always required on the vector used in the modification and to demonstrate that the new genes are inserted in a stable way. . If the GM micro-organism is consumed in a viable form, information on it's behaviour and lack of pathogenicity is also carefully assessed.

vii) GM plants

21. The assessment of the safety of foods derived from GM plants is carried out in comparison with the non-GM counterparts that they would replace. In doing this, the natural variation in the composition of plants and in the foods derived from plants, due to climatic and other environmental factors is taken into account as far as is possible. Information is therefore assessed on the composition (major nutrients, including vitamins and other beneficial components) and agronomic behaviour (growth patterns, flowering time and yield, both with and without application of herbicides in the case of herbicide-tolerant GM plants) of GM plants grown at several sites. This information is evaluated in comparison with that obtained on non-GM plants grown at the same time. These data are needed to demonstrate that the GM plant falls within the natural variation seen for the non-GM counterpart, except for any intended effects of the modification. The assessment also considers the nature of the genetic modification and includes a detailed characterisation of the inserted genetic material . The approach taken to date has been based on a case-by-case evaluation of each individual GM food so that any unintentional effects of the particular modification can be assessed. The ACNFP is not prepared at this stage to consider any blanket clearance of particular gene sequences .

22. Traditional plant breeding, which involves the random recombination and shuffling of genes via sexual reproduction, and subsequent selection of plants showing desirable characteristics, can also results in changes in the food derived from these plants. Many non-GM plant crops now being grown contain natural disease and herbicide resistance genes bred from wild relatives. Some crops developed by traditional plant breeding that are currently being grown are also herbicide tolerant. Novel sources of breeding materials have been used to supply traits for resistance to pests and disease to bypass the barriers to sexual crosses between unrelated species. If incompatible plants are cross pollinated, the seed will normally not develop fully. However, the immature seed can be removed from the plant and grown in the laboratory, thus overcoming this barrier. The safety of food produced from such plants are not subject to the same degree of scrutiny as those derived from plants altered using genetic modification.

viii) Ethical issues

23. The genetic modification of food may raise ethical questions for some people. This topic was considered in the UK in 1993 by a Committee chaired by the Reverend Polkinghorne, (who was at that time a member of the ACNFP). This

committee recommended that GM foods that contained copy genes of human origin should be labelled so that consumers can make informed choices about the foods they eat . In addition it was recommended that the presence of copy genes from animals that are the subject of dietary restrictions by religious groups should also be labelled. It was also accepted that vegetarians may also wish to know if any copy genes of animal origin are present.

ix) Provision of data

24. It has been suggested that the safety of individual GM foods should not be assessed on the basis of data submitted by the company that developed the food, but should be based on independent data. However, the data submitted to support applications for approval has to be produced to appropriate standards of Good Laboratory and, where relevant, Good Clinical, Practice. This is common practice in many areas of chemical safety evaluation. Any laboratories conducting such studies are subject to regular inspections to ensure that operating procedures are satisfactory and individual studies may be audited to ensure compliance with such procedures. Thus data produced to these standards is considered to be effectively independent.

25. Applicants are encouraged to deposit all the detailed information in the British Library so that it is available for scrutiny by interested parties. Work is currently underway to consider how safety data on GM foods could be made further available to the public.

Annex C

INTERNATIONAL ACTIVITIES

1. In the USA, the Food and Drug Administration (FDA) has responsibility for overseeing the safety of food under the Federal Food Drug and Cosmetics Act (FFDCA) which places the onus on a producer to ensure food is safe. Under the Act the only foods which require specific approval by the FDA are food additives. The act requires that food additives go through an approval process unless they are considered to be Generally Recognised As Safe (GRAS). GRAS status is demonstrated either by a long history of consumption prior to 1958 or if it is regarded as safe by scientific experts, based on publicly available scientific information. Foods which contain additives that have neither been specifically approved by the FDA nor have GRAS status are considered to be unsafe and their sale is illegal. The FFDCA contains 'adulteration' provisions which authorise the FDA to remove unsafe foods from the market and make producers legally responsible for the safety and wholesomeness of the foods they market.

2. In a policy statement on foods derived from new plant varieties, issued in 1992, the FDA concluded that the introduction of new biological techniques remained consistent with the characteristics that underpin the FFDCA. Namely that food safety is determined by the characteristics of the consumed or processed product rather than the method by which it was produced. In the policy statement the FDA concluded that existing food legislation can adequately address safety issues

relating to foods obtained from GM crops. The existing controls impose a clear legal duty on producers to ensure the safety of foods they offer to consumers. This legal duty is backed up by stringent FDA enforcement powers for product recalls and authority to require pre-market-reviews, and approval if necessary, to protect public health.

3. The statement makes it clear that substances introduced into food by way of plant breeding are considered to be 'added' and thus subject to the food additives provisions of the FFDCA. That is, if they are not GRAS, they need to be approved before they can legally be sold. However, since most transgenes and their associated proteins have a history of food use they would be classified as GRAS. The FDA policy statement concluded that a special review of a genetically modified food would only be needed if the food raised safety concerns. In order to clarify when an evaluation may be required the FDA policy statement identified the following situations as indicators that could trigger an evaluation:

- Unexpected Effects (produces unexpected genetic effects)
- Known Toxicants (has significantly higher levels of toxicants than present in other edible varieties of the same species)
- Nutrients (significantly altered levels of important nutrients)
- New Substances (differs significantly in composition from such substances currently found in food)
- Allergenicity (contains proteins that cause an allergic response)
- Antibiotic Resistance Selectable Markers (contains marker genes that theoretically may reduce the therapeutic effects of clinically useful antibiotics)
- Plants Developed to Make Speciality Non-food Substances (plants developed to make substances like pharmaceuticals or polymers that will also be used for food)
- Issues Specific to Animal Feeds (significant changes in nutrients or toxicants)

4. Although most GM foods do not require specific approval, the FDA encourages companies to notify details of their products on a voluntary basis. The emphasis remains on the company conducting a safety assessment of the product and communicating the results of the assessment to the FDA. To assist companies assess the safety of their products the FDA has developed a series of decision trees, which focus the evaluation on the differences between the new variety and its unmodified equivalent. This approach is consistent with the concept of substantial equivalence developed by the OECD.

5. The 1992 policy statement by the FDA indicated that consultations are an appropriate forum for industry and the FDA to address scientific and regulatory issues prior to marketing. Once any necessary consultation has been concluded and safety and regulatory issues have been resolved the FDA recommend that the product developer should submit to the FDA a summary of the safety and nutritional assessment of the product and make a scientific presentation of the data supporting the safety assessment to FDA scientists. The emphasis placed on the desirability of early pre-market consultations has so far been followed by all companies developing GM foods. Details of GM crops that have completed the regulatory process in the USA are given in table 1, overleaf.

6. The products are grouped by the year in which their consultations were completed. The trait introduced into the variety as well as the origin and identity of the introduced gene responsible for the trait are given. Note that the listed products may have pending regulatory issues with EPA or USDA/APHIS.

Labelling

7. The 1992 FDA policy statement also addresses the labelling of foods obtained from new plant varieties. The FDA philosophy is that genetic modification techniques do not result in foods that differ as a class from foods developed through other methods of plant breeding, thus there is no need to label the technique used to produce the food. Provided the company's safety assessment demonstrates that there are no unacceptable differences between the GM variety and the conventional equivalent with respect to toxicants, allergens or nutritional value, no labelling is required. Labelling is required in situations where a food obtained from a GM variety differs from that obtained from a conventional counterpart in such a way that the usual name would be misleading. Labelling would also be required if the modification gave rise to safety issues to which the consumer should be alerted.

Firm	New Variety	Trait Gene & Source
1998		
AgrEvo, Inc.	Glufosinate tolerant soybean	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
	Glufosinate tolerant sugar beet	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
	Insect protected and glufosinate tolerant corn	The <i>cry9C</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>tolworthi</i> and the bar gene from <i>Streptomyces hygrosopicus</i> .
	Male sterile or fertility restorer and glufosinate tolerant canola	The male sterile canola contains the barnase gene and the fertility restorer canola contains the barstar gene from <i>Bacillus amyloliquefaciens</i> . Both lines have the phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
Calgene Co.	Bromoxynil tolerant/insect protected cotton	Nitrilase gene from <i>Klebsiella pneumoniae</i> and the <i>cryIA(c)</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> .
	Insect protected tomato	The <i>cryIA(c)</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> .
Monsanto Co.	Glyphosate tolerant corn	A modified enolpyruvylshikimate-3-phosphate synthase gene from corn.
	Insect and virus protected potato	The <i>cryIIIA</i> gene from <i>Bacillus thuringiensis</i> (Bt) sp. <i>tenebrionis</i> and the Potato Leafroll Virus replicase gene.
	Insect and virus protected potato	The <i>cryIIIA</i> gene from <i>Bacillus thuringiensis</i> (Bt) sp. <i>tenebrionis</i> and the Potato Virus Y coat protein gene.
Monsanto Co./Novartis	Glyphosate tolerant sugar beet	The enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4, and a truncated glyphosate oxidoreductase gene from <i>Ochrobactrum anthropi</i> .
Pioneer Hi-Bred	Male sterile corn	The DNA Adenine methylase gene from <i>Escherichia coli</i> .
University of Saskatchewan	Sulfonylurea tolerant flax	Acetolactate synthase gene from <i>Arabidopsis</i> .
1997		
AgrEvo, Inc.	Glufosinate tolerant canola	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
Bejo Zaden BV	Male sterile radicchio rosso	The barnase gene from <i>Bacillus amyloliquefaciens</i> .
Dekalb Genetics Corp.	Insect protected corn	The <i>cryIA</i> © gene from <i>Bacillus thuringiensis</i> (Bt).
DuPont	High oleic acid soybean	Sense suppression of the GmFad2-1 gene which encodes a delta-12 desaturase enzyme.

Seminis Vegetable Seeds	Virus resistant squash	Coat protein genes of cucumber mosaic virus, zucchini yellow mosaic virus, and watermelon mosaic virus 2.
University of Hawaii/Cornell University	Virus resistant papaya	Coat protein gene of the papaya ringspot virus.
1996		
AgriTope Inc.	Modified fruit ripening tomato	S-adenosylmethionine hydrolase gene from <i>E. coli</i> bacteriophage T3.
Dekalb Genetics Corp.	Glufosinate tolerant corn	Phosphinothricin acetyl transferase gene from <i>Streptomyces hygroscopicus</i> .
DuPont	Sufonylurea tolerant cotton	Acetolactate synthase gene from tobacco, <i>Nicotiana tabacum</i> cv. <i>Xanthi</i> .
Monsanto Co.	Insect protected potato	The <i>cryIIIA</i> gene from <i>Bacillus thuringiensis</i>
	Insect protected corn	The <i>cryIA(b)</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> .
	Insect protected corn	The <i>cryIA(b)</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> .
	Glyphosate tolerant/insect protected corn	The enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. strain CP4 and the glyphosate oxidoreductase gene from <i>Ochrobactrum anthropi</i> in the glyphosate tolerant lines. The <i>CryIA(b)</i> gene from <i>Bacillus thuringiensis</i> subsp. <i>kurstaki</i> in lines that are also insect protected.
Northrup King Co.	Insect protected corn	The <i>cryIA(b)</i> gene from <i>Bacillus thuringiensis</i> (Bt) subsp. <i>kurstaki</i> .
Plant Genetic Systems NV	Male sterile and fertility restorer oilseed rape	The male sterile oilseed rape contains the barnase gene from <i>Bacillus amyloliquefaciens</i> ; the fertility restorer lines express the barstar gene from <i>Bacillus amyloliquefaciens</i> .
	Male sterile corn	The barnase gene from <i>Bacillus amyloliquefaciens</i>
1995		
AgrEvo Inc.	Glufosinate tolerant canola	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
	Glufosinate tolerant corn	Phosphinothricin acetyltransferase gene from <i>Streptomyces viridochromogenes</i> .
Calgene Inc.	Laurate canola	The 12:0 acyl carrier protein thioesterase gene from California bay, <i>Umbellularia californica</i> .
Ciba-Geigy Corp.	Insect protected corn	The <i>cry1A(b)</i> gene from <i>Bacillus thuringiensis</i> <i>kurstaki</i> .
Monsanto Co.	Glyphosate tolerant cotton	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. Strain CP4.
	Glyphosate tolerant canola	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. Strain CP4.
	Insect protected cotton	The <i>cryIA(c)</i> from <i>Bacillus thuringiensis</i> (Bt) subsp. <i>kurstaki</i> .

1994		
Asgrow Seed Co.	Virus resistant squash	Coat protein genes of watermelon mosaic virus 2 and zucchini yellow mosaic virus.
Calgene Inc.	Flavr Savr™ tomato	Antisense polygalacturonase gene from tomato.
	Bromoxynil tolerant cotton	A nitrilase gene isolated from <i>Klebsiella ozaenae</i> .
DNA Plant Technology Corp.	Improved ripening tomato	A fragment of the aminocyclopropane carboxylic acid synthase gene from tomato.
Monsanto Co.	Glyphosate tolerant soybean	Enolpyruvylshikimate-3-phosphate synthase gene from <i>Agrobacterium</i> sp. Strain CP4.
	Improved ripening tomato	Aminocyclopropane carboxylic acid deaminase gene from <i>Pseudomonas chloraphis</i> strain 6G5.
	Insect protected potato	The <i>cryIIIA</i> gene from <i>Bacillus thuringiensis</i> (Bt) sp. <i>tenebrionis</i> .
Zeneca Plant Science	Delayed softening tomato	A fragment of the polygalacturonase gene from tomato.

Table 1 GM crops completing regulatory process in USA as of 8 January 1998

Source: US FDA

Canada

8. A request for the evidence relied upon to establish the safety of a novel food permits Health Canada to conduct a safety assessment for the subject product prior to authorizing its sale. Details of the safety assessment criteria adopted by Health Canada have been published in 'Guidelines for the Safety Assessment of Novel Foods, Volume II, Food Directorate, 1994'. The safety assessment criteria incorporates the food safety assessment concept enshrined in the OECD's principle of substantial equivalence.

9. Information on plants with novel traits that have been submitted for approval in Canada is available on the Internet at:

<http://www.cfia-acia.agr.ca/english/plant/pbo/okays.html>

Annex 6 - LABELLING OF GM FOODS

Current requirements in EU

1. The novel foods regulation contains rules for the labelling of GM foods, although they are written in rather general terms. Detailed rules (EC Regulation 1139/98) for the labelling of ingredients obtained from GM soya and maize came into force on 1

September 1998. These are seen as setting a precedent for all future novel foods. The regulation, which was unanimously agreed by all member states and the European Parliament, requires clear labelling where genetically modified material (DNA or protein arising from the modification) is present in the final foodstuff as sold to consumers. In the case of highly refined products such as soya and maize oils, which contain no genetic material, and are indistinguishable from the oils obtained from conventional soya and maize, the European Community considered that labelling would not convey any meaningful information about the composition of the final food. In addition a labelling requirement under such circumstances would be unenforceable. Where there is any reason to believe that GM material may be present, the food must be labelled as GM.

2. Regulation 1139/98 was recently amended by EC Regulation 49/2000 to include a 1% threshold and to extend the regulations to cover food sold to mass caterers. The amendments were adopted on 10 January 2000 and came into effect on 10 April 2000. The aim of such a threshold is to ensure that food ingredients obtained from non-GM sources do not need to be labelled as GM if they contain low levels of GM material as a result of adventitious contamination. Steps should be taken to keep the level of adventitious contamination in non-GM supplies to a minimum. The threshold only applies to ingredients obtained from non-GM sources - there will be no threshold for supplies obtained from sources of unknown origin. Companies will need to demonstrate to enforcement authorities that their ingredients are of non-GM origin; and it is possible that the use of documented/audited identity preservation systems could satisfy this requirement.

3. The threshold is applied to maize and soya ingredients and not the final food; the level in the final food will be much lower. The UK accepted that a figure of 1% represents the lowest level that is both enforceable and achievable in practice at the present time. We have however, asked for it to be reviewed within two years in the expectation that significant improvements will have been made in analytical methods and the supply situation by then to enable it to be reduced.

Animal feed labelling

4. Whilst there are extensive EC rules on animal feeds, none specifically relate to the use of GM materials in or as feedingstuffs. The UK and other Governments have therefore been pressing the Commission to publish its proposed Regulation covering novel animal feeds. This is expected to include labelling rules to be applied consistently in the EU. In the meantime MAFF has been exploring the possibility of voluntary national labelling arrangements; and a meeting with representatives of the feed industry, farmers and the multiple food retailers revealed a need for consistency and clarity in any terms used. ACAF has now sought views from interested parties on this aspect as part of a wider review of feed labelling issues.

5. ACAF is concerned with labelling the feed for the benefit of farmers and other purchasers. Inevitably however some representations will focus on whether animal products as sold to the ultimate food consumer should be labelled according to the presence or absence of GM material in feed. Such comments will be directed to the listening initiative, launched by Baroness Hayman on 21 January, on what

consumers want to see on food labels. A continuing issue here is the extent to which individual supermarket chains seek the removal of GM material from animal feed in order to make related claims for the meat, milk and eggs in their stores.

Enforcement

6. As with all food labelling legislation, enforcement responsibility rests with local authorities. On April 10, the Genetically Modified and Novel Foods (Labelling) (England) Regulations 2000 came into force. These regulations consolidate all enforcement legislation for GM labelling rules into a single piece of legislation.

Annex 7 - THE HUMAN GENETICS COMMISSION AND THE AGRICULTURE AND ENVIRONMENT BIOTECHNOLOGY COMMISSION

1. Broadly, their terms of reference for both Commissions are to give advice to Ministers on the wider picture and act as a focus for public debate in respect of biotechnology. In particular, they will:

- undertake strategic analysis including looking into the future to see how biotechnology might develop in their areas of responsibility;
- look at the lessons learned from individual cases requiring regulatory decision to build up a wider picture;
- advise on changes which Ministers might wish to make to the guidelines which regulatory bodies are required to follow;
- address broader issues regarding the acceptability of GM activities and relevant ethical considerations;
- identify any gaps in the regulatory and advisory framework, taking account of new developments and European and global dimensions; to advise Ministers whether existing committees should continue or new ones should be set up; and to advise on the mix of expertise which committees should contain; and
- involve and consult stakeholders and the public. This will be an essential aspect of their work and they will be asked to undertake regular public consultation on the issues that they are considering.

2. The new commissions will maintain close contact with the work of the regulatory bodies. However, they will not be involved in case-by-case assessment of individual applications for new products or processes. This will continue to be undertaken by the existing scientific advisory committees such as the ACNFP and ACAF. In reviewing the advice from the strategic commissions, Ministers may decide to alter the guidelines or terms of reference of the current bodies or seek changes to the EC regulatory system.

3. Considering and advising on the best way to address public concerns will be a core element of the work of the new commissions. One key message to emerge from the public consultation was that the current arrangements for the regulation of biotechnology are difficult to understand, and that they do not take sufficient account

of the views of all potential stakeholders and the public. Each Commission therefore has a clear mandate to conduct regular public and stakeholder consultation on the issues they consider. The Board of the FSA will be expected to undertake a similar role in respect of GM food and feed issues.

Annex 8 - CHAIRMAN'S REPORT OF THE OECD CONFERENCE

GM FOOD SAFETY: FACTS, UNCERTAINTIES AND ASSESSMENT

GM FOOD SAFETY: FACTS, UNCERTAINTIES, AND ASSESSMENT
The OECD Edinburgh Conference on the Scientific and Health Aspects of Genetically Modified Foods. 28 February - 1 March 2000

LA SÉCURITÉ DES ALIMENTS GÉNÉTIQUEMENT MODIFIÉS : FAITS,
INCERTITUDES ET ÉVALUATION
Conférence OCDE d'Edimbourg sur les aspects scientifiques et sanitaires des aliments génétiquement modifiés. 28 février - 1er mars 2000

INTRODUCTION

1. The conference was attended by about 400 invitees from more than 25 countries. Its aim was to be inclusive, and to encourage a wide diversity of views to be expressed both on the platform and in the audience. Each session was organised with short introductory presentations, followed by commentaries from panel discussants before opening the discussion to the audience.
2. The speakers and panellists were, in approximately equal numbers, proponents of GM, opponents, and those who were essentially neutral. The presenters came from a wide range of developing and developed countries. They were primarily scientists, regulators, NGOs and industry representatives.
3. The conference focused on GM food safety and human health. In my Introduction, I acknowledged that this was only one part of the debate about GM technology in food and agriculture, which in turn was only part of the debate about the future of biotechnology. Whilst the conference was focused on food safety, which was the primary public and NGO concern in the UK and elsewhere during the adverse public reaction to GM last year, I did not wish to exclude debate of other issues. These include ethics, environmental safety, economic development, and the ownership of intellectual property.
4. The conference also focused on the science (including the social science of consumer attitudes) of GM food safety, although I agreed that other non-scientific issues (e.g. values and beliefs) come into the debate, and should not be excluded.
5. The conference was not aimed at producing a simple consensus, but rather at identifying areas of greater agreement, of divergence of opinion, and of uncertainty due to lack of knowledge. Even the very basic question of whether or not GM

technology is fundamentally different from genetic modification through conventional breeding was one on which there was not a consensus amongst the participants.

6. The conference was divided into three sections:

- (a) What is the science of GM and its potential risks and benefits for food and agriculture?
- (b) What is the science of assessment of food safety, and what, if any, are the special problems posed by GM foods?
- (c) What are the regulatory systems worldwide, and do these require adjusting because of special features of GM foods?

7. This short summary provides an account of my personal impressions of the conference. A more detailed summary is available in the rapporteurs' report. I have taken into account comments made in the concluding discussion, and afterwards by e-mail and by members of the Steering Committee.

PRINCIPAL CONCLUSIONS

Food safety

8. Worldwide, many people are eating GM foods (especially in North America and China) with no adverse effects on human health having been reported in the peer-reviewed scientific literature.

9. There could, in theory, be long-term effects on human health that have not yet been detected because GM foods have been available for less than ten years.

Decision-making, assessment and choice

10. In the future, policy decisions about GM food, as well as the assessment of their safety, should be more inclusive and open than has typically been the case in the past. People want to know how decisions have been reached and to be consulted. This process will help to remove suspicion.

11. Having said this, there was no clear conclusion on how attitudes and beliefs that might become apparent as a result of consultation should be incorporated into the assessment and communication of GM food safety. For many, safety assessment remains an essentially technical and scientific process.

12. Consumers should be allowed to choose. Labelling of GM foods is important, although there was no agreement on how far this should extend (e.g. to GM derivatives? To animals fed on GM?). It is important also to note that the labelling applies to the process by which organisms are created and not the food product, which in many cases is identical to its conventional counterpart.

The assessment of GM food safety

13. The assessment of the safety of any novel food, including GM food, involves a variety of kinds of evidence. One commonly used tool is the concept of "substantial equivalence". The essence of this idea is that a comparison between the novel food

and one already in the diet provides the basis for asking questions about the safety of the novel product. Substantial equivalence is not a quantitative criterion or a hurdle, but a framework for thinking. It is continually modified and updated, but it is timely now, after six years of using the tool, to undertake a more detailed review.

14. On two more technical issues, (a) there is no clear agreement about the importance of animal feeding trials (other than toxicity trials) in assessing the safety of novel foods, including GM foods; (b) The methods for testing toxicity and allergenicity of GM foods need re-examination.

15. Existing international bodies are working to achieve consistent standards and criteria for the assessment of food safety, and this is to be applauded. The precautionary principle is now beginning to be discussed internationally in relation to food safety, but it has not yet been translated into an agreed operational form.

GM technology in developing and developed countries

16. The majority of speakers from developing countries stressed the crucial importance of GM technology as part of the armoury for feeding their population in the future. In China, with 20% of the world's population and 7% of the land surface, GM is already playing a major role in food production, and its importance was also emphasised by speakers from Africa and Latin America. However, the view was also expressed that the future application of GM technology in developing countries should be more explicitly tuned to the needs of local people rather than of multinational corporations.

17. In light of this last comment, GM technology for the developing world should be carried forward through a mixture of public and private funding.

18. Whilst it is essential that standards of safety assessment should be consistent and high throughout the world, the strongly expressed demand for GM technology in developing countries casts substantial doubt on proposals for a worldwide moratorium made by some participants.

19. The first generation of GM crops and foods are perceived as having brought little direct benefit to consumers in developed countries, but this may well change as new products appear with direct quality, health or price benefits.

Concerns about GM other than food safety

20. The principal concerns of the opponents of GM related less to food safety than to the broader question of why GM food is being produced at all. Most developing country speakers argued forcefully that GM technology is an essential part of their future food production (see paragraph 16), but this was rejected by some NGO speakers from Europe and North America. They argued, instead, for solving world food shortage by redistribution, better prevention of loss during storage and so on. They also pointed out, as did some developing country participants, that citizen engagement in decision-making and discussion (see paragraph 10) should be improved in developing countries.

21. A second concern about GM agriculture was the potential environmental impact. Although there have been many field trials and, in some parts of the world, large-

scale commercial planting of GM crops, there has been insufficient work to fully assess environmental impacts, especially in the biodiversity-rich tropics.

THE WAY FORWARD

22. The most significant aspect of the Edinburgh Conference was that it included all sides of the debate surrounding GM foods and nevertheless identified certain areas of agreement. It also succeeded in identifying issues in which there is disagreement or uncertainty due to lack of knowledge, and in separating out issues which are subject to scientific analysis and those which are related to political factors, beliefs and values. Further detail is available in the rapporteurs' report.

23. The conference represents a new start in the global debate about GM food and agriculture: a more inclusive approach in which the protagonists discussed some of the key issues with each other. There was support for continuation of this process to deal with other parts of the debate.

24. I therefore recommend that an **international forum** be set up to continue the process started in Edinburgh. The aim of such a forum would be to provide governments with a state of the art assessment of scientific knowledge about GM technology, and to set this assessment in the context of broader concerns of society.

25. A model for such a global assessment is the IPCC (Intergovernmental Panel on Climate Change). This Panel allows governments to draw on worldwide expertise in climate science. It informs but does not make policy and it acknowledges the minority scientific views as well as the current majority view. It also updates its reports at intervals.

26. The forum I propose would have similarities to the IPCC, but it would include not only scientists but also other stakeholders.

27. The following suggestions indicate how the forum might be developed:

(a) It should build on and interact with, rather than duplicate or replace, the work of existing international groups such as Codex Alimentarius.

(b) It should be global in scope and not restricted to G8 countries or a subset thereof. In particular, a key message of the Edinburgh conference was the role of developing countries where application of the technology is proceeding rapidly.

(c) It should be led by the world's best scientific experts, but include a wider range of expertise and opinion than scientists.

(d) Two initial themes for the forum would be food safety and environmental safety of GM in agriculture and food production.

(e) There would be two kinds of outputs: (a) scientific assessments in the form of reports that inform policy; (b) an inclusive and global debate about the relationship between GM technology and society. It will be essential that governments take ownership of the forum and its reports.

(f) The reports should be produced in a timely way so as to facilitate the assessment of rapidly emerging technologies.

SUMMARY

28. In summary, this proposed forum could serve two important functions by enabling a global debate and assessment of GM technology in food and agriculture.

29. First, it will allow the best scientific analysis of the risks and benefits of the new technology, as it develops, to be carried out in order to provide governments worldwide with appropriate expert advice. This advice will acknowledge the range of scientific opinion and uncertainties, as well as indicating the current majority opinion.

30. Second, it could create a better understanding of the relationship between technological developments, policy, and the concerns and aspirations of citizens. This would be achieved by widening the forum beyond purely scientific analysis, to include the broader issues that I have referred to in relation to the Edinburgh conference.

31. There is more than one way of achieving these twin objectives. One approach would be to have an expert panel, led by scientists but including other stakeholders, to carry out the scientific assessments. Draft reports of this expert panel could be used as the basis for discussion by a broader forum, along the lines of the Edinburgh meeting, in which the non-science issues are brought into the debate. The expert panel might choose to revise its report in light of this broader discussion.

32. I have deliberately left the details of implementation to others, because I want to sketch out the vision rather than the detailed mechanisms.

John Krebs
Oxford