

HEALTH IMPLICATIONS OF GENETICALLY MODIFIED FOODS

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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 diabetic 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 soil 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 guns 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 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 researchers to show possible DNA uptake. Under certain conditions, direct feeding of free DNA (obtained from bacteriophages) 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 transformation or via natural vectors such as plasmids. 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 evidence 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 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-organisms 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. Studies 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.

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.

List of technical notes available on request

A List of products considered by the ACNFP

B Technical Note on the History of the UK ACNFP Guidelines for the Safety Assessment of Novel Foods and development of guidance from the European Commission and issues considered during the safety assessment of individual GM foods

C International activities