

**ACNFP**

# **Advisory Committee on Novel Foods and Processes**

**Annual Report 1998**

**Ministry of Agriculture,  
Fisheries and Food**

**Department of Health**

**ACNFP**

# **Advisory Committee on Novel Foods and Processes**

Annual Report 1998

The Advisory Committee on Novel Foods and Processes (ACNFP)  
is an independent body of experts whose remit is:

*‘to advise Health and Agriculture Ministers of Great Britain and the Heads of the Departments of Health and Social Services and Agriculture for Northern Ireland on any matters relating to the irradiation of food or to the manufacture of novel foods or foods produced by novel processes having regard where appropriate to the views of relevant expert bodies’.*

# Contents

	Page
<b>Foreword</b>	<i>vii</i>
<b>Introduction</b>	<i>viii</i>
<b>1. The EC Novel Foods Regulation (258/97)</b>	<b>1</b>
The Regulation	
Implementing the Regulation: full and substantial equivalence applications	
Applications to the ACNFP under the previous voluntary scheme for the safety assessment of novel foods	
<b>2. Full applications made to the UK</b>	<b>4</b>
Processed products derived from GM tomatoes	
<b>3. Substantial equivalence applications made to the UK</b>	<b>6</b>
Insect protected GM cottonseed	
Herbicide tolerant GM cottonseed	
Cereal fractions	
<b>4. Applications made to other member states</b>	<b>8</b>
GM radicchio rosso and green hearted chicory (Netherlands)	
<i>Stevia rebaudiana</i> Bertoni (Belgium)	
Phospholipids from egg yolk (Belgium)	
<b>5. Other issues considered by the ACNFP</b>	<b>10</b>
Potential application	
Camelina Oil	
Fruitrim®	
Reports and other issues	<b>10</b>
Statistically valid data to support safety clearance of crops products under the Novel Foods Regulation	
Toxicological assessments of novel foods	
Letter from Chief Medical Officer concerning novel foods for infants	
Joint ACNFP/COMA ad hoc working group meeting on the dietary implications of cumulative nutritional changes in individual novel and conventional foods	
Risk Assessment: the role of advisory committees	
MAFF research and development report on gene transfer	
Royal Society statement on GM plants for food use	
Rowett Institute GM potatoes	
US Food and Drugs Administration (FDA) paper on antibiotic resistance marker genes (ARMs) in transgenic plants	
Joint ACNFP/Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) Seminar	
ACNFP consideration of Greenpeace reports	
Other papers for information	

	Page
<b>6. Other activities</b>	<b>14</b>
Improving transparency of the ACNFP	
ACNFP sub-group on post-market monitoring of novel foods	
<b>7. Developments elsewhere</b>	<b>15</b>
European Commission proposal for a directive on food irradiation	
Labelling of GM foods	
<b>8. Contact points</b>	<b>17</b>
<b>9. References</b>	<b>18</b>
<b>10. Glossary</b>	<b>20</b>
<b>11. Appendices</b>	
I ACNFP: remit, membership and list of members' interests, code of conduct, interaction with other committees.	23
II UK Competent Authority initial assessment report on the safety assessment of processed products from genetically modified tomatoes derived from line TGT7F: final report sent to the European Commission.	34
III Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to GM chicory.	44
IV Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to products from <i>Stevia Rebaudiana</i> Bertoni.	46
V Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to Phospholipids from Egg Yolk.	48
VI Letter to European Commission containing the UK Competent Authority decision on camelina oil.	49
VII Letter to European Commission containing the UK Competent Authority decision on Fruitrim®.	51
VIII Statistically valid data to support safety clearance of crop products under the Novel Foods Regulation.	53
IX The role of toxicological studies in assessing the safety of novel foods for humans.	56
X Note of the meeting of the joint ACNFP/COMA ad hoc working group meeting on the dietary implications of cumulative nutritional changes in individual novel and conventional foods.	60
XI Letter from ACNFP to US Food and Drugs Administration (FDA) paper on 'Guidance for industry: use of antibiotic resistance marker genes in transgenic plants'.	64

	Page
XII Health and environmental risks of genetically modified soya: food safety issues considered by the ACNFP.	72
XIII ACNFP response to the Greenpeace report 'Genetic Engineering: too good to go wrong'.	69
<b>12. Cumulative index</b>	<b>76</b>

# Foreword

This tenth annual report of the Advisory Committee on Novel Foods and Processes is written after the first complete year under my Chairmanship and also the first full year since the EC Novel Food Regulation (EC) 258/97 came into force in May 1997.

The primary role of the Committee continues to be the safety assessment of novel foods and processes that are submitted to it. In order to do this, all committee members play a full part in the safety assessment process and in considering related issues, with the ethical and consumer representatives on the Committee making a major contribution to the discussions.

The public debate relating to GM foods has continued unabated throughout the year. The difficulties encountered in assessing risk where the risk is very low and explaining this in a meaningful way to consumers present a demanding challenge. There continues to be a great deal of inventive media coverage, which has led consumers to become concerned that scientific opinion is not consistent either within the UK or across other Member States. Consumers are well aware of the global nature of the food chain and differences in public attitudes to food and acceptance of new technologies across the world.

I believe that we have a robust and rigorous approach to the approval process. The Committee will continue to seek satisfactory clarification of all scientific issues that members raise before making recommendations to Ministers, where appropriate, to grant approval to market a particular novel food. Our judgements must continue to be robust and conservative. We have been accused of over-caution but we must never deviate from this approach if we are to engender public confidence.

As a result of the public interest generated, I and other committee members spend a considerable amount of time writing articles or speaking to consumer groups, scientific conferences, non-governmental agencies, the press and the broadcast media. I continue to believe that it is essential that important issues such as these are the subject of balanced and informed debate. To this end, I am also committed to increasing the transparency of the working of the Committee. One important way to do this is to hold open meetings on key generic issues (see Section 6). It is important for the ACNFP to work actively with other advisory committees and meetings have been held with the Committee on Medical Aspects of Food and Nutrition Policy (COMA) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT). There also continues to be cross membership of the various committees dealing with issues related to novel foods. A further step this year was a joint meeting of advisory committee chairpersons held by the Government's Chief Scientific Advisor, Sir Robert May. Dialogue across committees will continue to be essential to ensure that as technology continues to develop, all issues are considered.

*J M Bainbridge*

May 1999

# Introduction

This annual report of the Advisory Committee on Novel Foods and Processes (ACNFP) covers the first complete year since the EC Novel Foods Regulation (258/97) came into force in May 1997. As a result of changes to the way that applications are brought before the ACNFP, the format of the annual report has been updated. The report begins with a brief summary of the Novel Foods Regulation, the differences between full and substantial equivalence applications and a summary of the previous voluntary safety assessment scheme for novel foods, which was in operation before the Novel Foods Regulation came into force.

The ACNFP received a number of applications in 1998, details of which can be found in Sections 2, 3 and 4 of this report. The summary reports of applications discussed by the ACNFP in 1998 have been split into three sections; applications for full assessments initially received by the UK Competent Authority; substantial equivalent applications received by the UK; and those received where another Member State has supplied the initial opinion on a full application.

Two meetings of the ACNFP sub-group on the post market monitoring of novel foods were held in 1998, and as part of the ACNFP's ongoing aim to increase the transparency of its workings, invited observers from interested groups were present. Details of the discussions are outlined in Section 6 of the report.

After much debate about the labelling of GM soya and maize, an EC Regulation came into force on 1 September 1998. This made the labelling of GM soya and maize mandatory where DNA or protein resulting from the modification is present. Also in 1998, agreement was reached on a final text for the EC Directives on Food Irradiation. Details of both are contained in Section 6 of the report.

Copies of previous annual reports <sup>1-9</sup> can be obtained from the MAFF Secretary to the Committee (see Section 8). A cumulative index of topics considered in previous annual reports can be found on page 76.



# 1 The EC Novel Foods Regulation (258/97)

## The Regulation

- 1.1 On 15 May 1997, Regulation (EC) 258/97 of the European Parliament and of the Council concerning Novel Foods and Novel Food Ingredients<sup>10</sup> came into effect introducing a statutory pre-market approval system for novel foods throughout the European Union. This Regulation is directly applicable and legally binding in all Member States, and in the UK replaced the voluntary scheme for the assessment of novel foods which had been in operation for more than 10 years. Under the EC Novel Foods Regulation, companies wishing to market a novel food in the EU are required to submit an application to the Competent Authority in the Member State where they first intend to market their product. In the UK the Competent Authority is provided by MAFF and the Department of Health working jointly but is likely to eventually be provided by the Food Standards Agency.

The Regulation defines a novel food as one which has not been used for human consumption to a significant degree within the Community and which falls under one of the following categories:

- a) foods and food ingredients containing or consisting of GMOs within the meaning of Directive 90/220/EEC;
- b) foods and food ingredients produced from, but not containing GMOs;
- c) foods and food ingredients with a new or intentionally modified primary molecular structure;
- d) foods and food ingredients consisting of or isolated from micro-organisms, fungi or algae;
- e) foods and food ingredients consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagation or breeding practices and having a history of safe food use;
- f) foods and food ingredients to which has been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances.

Where there is any doubt whether a food is novel or not, the EC Standing Committee for Foodstuffs will decide.

## Implementing the Regulation: full and substantial equivalence applications

- 1.2 The implementation of the EC Novel Foods Regulation has brought changes to the ACNFP and the way that it operates. Although most applications are discussed at a formal meeting, due to the statutory time limits imposed by the Regulation (i.e. 90 days for initial opinion and 60 days for assessment of opinions expressed by other Member States), it has been necessary for consideration of some applications to be completed between meetings. A computerised discussion system was developed to facilitate a full discussion by Members

of applications and other issues that arise between meetings, although the committee's conclusions are published in the usual way.

The safety assessment of novel foods follows a comparative approach set out by the EC guidelines<sup>11</sup> (details of which are available from the Stationary Office or the ACNFP Secretariat, see page 17). Wherever possible, the novel food is compared with an existing counterpart, which it may replace in the diet. Differences between a novel food and its counterpart are identified and undergo a detailed examination in order to establish whether the novel food is as safe as its conventional counterpart.

For a full safety assessment, companies are required to submit an application to the appropriate Competent Authority in the Member State where they first intend to market the product. A copy of the application must also be sent to the European Commission. Once a Competent Authority has accepted an application, it has 90 days in which to complete an initial safety assessment and forward it to the Commission. The Commission must then copy the assessment to other Member States for their comments which have to be made within 60 days. If the initial assessment is favourable and no objections are raised by other Member States, then the food product can be marketed. If objections are raised, or if the initial Member State considers that an additional assessment is required, the application will be referred to the EC Standing Committee for Foodstuffs for final agreement, consulting the EC Scientific Committee for Food as necessary.

Under the Novel Foods Regulation, products are assessed for safety with the aid of the concept of substantial equivalence. The concept of substantial equivalence is an internationally accepted approach to the assessment of food safety, particularly foods produced by modern technology. It was formulated by the World Health Organisation and developed by the Organisation for Economic Co-operation and Development. The concept codifies the idea that if a food or food ingredient under consideration can be demonstrated to be essentially equivalent in composition to an existing food or food ingredient then it can be considered that a new food is as safe as the conventional equivalent. The levels and variation for characteristics in the novel food must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of data. For food ingredients that are considered to be substantially equivalent to existing foods, the company must supply evidence that supports its view. This evidence can be based upon the opinion of a Member State or on generally available and recognised scientific evidence.

The ACNFP looked at the issue of notifications in December 1997 which could be considered under the route of substantial equivalence. They concluded that in their opinion, for food ingredients derived from GM crops, only those which contained no DNA or protein and which were not therefore themselves genetically modified would be suitable for considering under such a procedure. This approach has now been agreed by the Standing Committee for Foodstuffs.

All other ingredients derived from GM crops where novel DNA or novel protein may be present (as a result of less intensive processing compared with refined foods) would not be able to be assessed under this procedure and would require an application for full safety assessment to be made.

## **Applications to the ACNFP under the previous voluntary scheme for the safety assessment of novel foods**

- 1.3 A number of products were considered by the ACNFP under the voluntary safety assessment scheme, which operated before the EC Novel Foods Regulation (258/97) came into force in May 1997. A list of these is contained in the 1996 ACNFP annual report<sup>8</sup>. Those products known to have been marketed before May 1997 have been marked on this list with an asterisk. Copies can be obtained from the ACNFP Secretariat (see page 17).

Under the Novel Foods Regulation, even if a product had been previously cleared for food use, if it had not been marketed within the EU before May 1997, the product's safety would require reassessment. Products marketed prior to the introduction of the Novel Foods Regulation do not require reassessment by the ACNFP or other EU Competent Authority but remain, in the UK, subject to the provisions of the UK Food Safety Act (1990)<sup>12</sup>.

## 2 Full applications made to the UK

### Processed products derived from GM tomatoes

- 2.1 The ACNFP has previously considered submissions from Zeneca Plant Sciences seeking approval to market tomato paste produced from certain lines of GM tomatoes. The tomatoes were genetically modified to reduce the levels of a naturally occurring pectin-degrading enzyme, polygalacturonase (PG), such that fruit and processing quality was improved (see 1995 Annual Report<sup>7</sup>). In 1997, the Committee received a further submission seeking food safety clearance under the Novel Foods Regulation for peeled and comminuted processed tomato products produced from *hybrid* lines derived from the GM *inbred* line TGT7-F. The ACNFP had already evaluated and cleared these for the production of tomato paste under the UK's voluntary scheme for the safety assessment of novel foods. They had concluded that peeled and comminuted tomato products from these lines were as safe for human consumption as those derived from non-GM tomatoes (see 1997 Annual Report<sup>9</sup>).

Tomato paste produced from the GM tomatoes has been on sale in the UK since February 1996 and does not require further approval under the Novel Foods Regulation. However, not all the processed products produced from the GM tomatoes cleared under the UK's voluntary system were on sale in the EU prior to May 1997 when the EC Novel Foods Regulation (No. 258/97)<sup>10</sup> came into force. Therefore, the company submitted a full application in 1998 seeking approval to place on the market all processed tomato products derived from line TGT7F.

The GM tomato was genetically modified using *Agrobacterium tumefaciens* mediated transformation to insert a partial synthetic PG gene from the tomato variety 'Ailsa Craig', in the sense orientation, and the *nptII* gene originating from *Escherichia coli* as a selectable marker.

The GM tomatoes fall into category 3.1 of the European Commission's Guidelines on the Assessment of Novel Foods. This states that the host plant used for the genetic modification has a history of use as food or as a source of food in the Community under comparable conditions of preparation and intake. The Committee adopted a comparative approach in accordance with the Commission's Guidelines to establish whether the tomato products produced from GM tomato hybrids were as safe for human consumption as similar products produced from non-GM tomatoes. A full appraisal was carried out as the products did not fulfil the requirements for a substantial equivalence consideration (see Section 1.2).

The detailed information provided by the Company on the genetic modification procedure satisfied the Committee that no unintentional changes had taken place at the molecular level. Data on agronomic performance from field trials demonstrated the stability of the inserted genetic material over several generations under differing environmental conditions, and provided further reassurance that no unintended secondary changes had occurred.

Compositional analyses reviewed by the Committee demonstrated there were no significant differences between the processed products produced from the GM tomatoes and their non-GM counterparts. This was further evidence that no secondary effects had occurred as a result of the genetic modification.

*Detailed descriptions of underlined words are contained in the Glossary*

The ACNFP also considered the introduction of the *nptII* gene into the GM tomato. The Committee was satisfied with the information provided by the Company, that demonstrated that the thermal processing that the fruit undergoes to produce the final products, degrades both the gene and its protein product to a non-functional state.

The Company submitted a labelling proposal for the GM processed tomato products in accordance with Article 8 of Regulation 258/97 and other applicable labelling provisions in Community law. The proposed label on the processed tomato products will follow that already in use voluntarily on the cans of tomato paste on sale in two of the UK's supermarket chains. The proposed labelling is:

‘produced from genetically modified tomatoes’ or

‘made from genetically modified tomatoes’

Having considered all the data, the ACNFP was able to reaffirm its earlier conclusion that the processed products from the GM tomato line TGT7F were as safe for human consumption as non-GM tomato processed products. A copy of the Committee's report can be found at Appendix II. This was forwarded to the Commission on 4 June 1998 for circulation to other Member States under the 60- day procedure laid down in Article 6(4) of the Novel Foods Regulation. However, some member states raised objections to the initial assessment of the application, and the European Commission subsequently requested advice on it, from its scientific committee for food (SCF).

*At the time of going to press the SCF had not completed its assessment.*

## 3 Substantial equivalence applications made to the UK

### Insect protected GM cottonseed

- 3.1 A submission was received from Monsanto Europe SA late in 1997 seeking an opinion on the substantial equivalence of processed products (oils and linters) derived from GM cottonseed that had been modified to be resistant to insects. The initial opinion that further data were required before a final conclusion could be reached was described in the 1997 Annual Report<sup>9</sup>.

Further information supplied by the company was evaluated by the Committee during 1998. It was stated that the linters would not be used as such for food, but would be used as a source material for the production of food additives. They were thus outside the scope of the Novel Food Regulation, although such additives would need to be assessed in accordance with Community legislation on food additives. Therefore, the request for an opinion on substantial equivalence was only deemed to relate to oil produced from the GM cottonseed.

The Committee did not consider that the quality of the genetic data supplied was adequate. In addition, it agreed that analytical data were needed to demonstrate that neither the novel gene, nor its protein product, were present in the refined oil. Further information was also required to justify the methodology chosen for the compositional analyses of the oil. The Committee concluded that no decision could be reached on the substantial equivalence of oil obtained from this GM cottonseed line until this information had been received.

### Herbicide tolerant GM cottonseed

- 3.2 A submission was also received from Monsanto Europe SA seeking an opinion on the substantial equivalence of processed products derived from GM cottonseed that had been modified to produce the protein CP4 enolpyruvylshikimate-3-phosphate synthetase (EPSPS), which confers tolerance to the herbicide glyphosate. As for the application described above, the initial assessment of this request was described in the 1997 Annual report<sup>9</sup>. Further data supplied by the Company were assessed by ACNFP during 1998. Having considered this, the Committee expressed similar concerns to those for the insect protected cottonseed application and requested further information.

### Cereal fractions

- 3.3 A submission was received in 1997 under the voluntary scheme seeking clearance of a range of soluble and insoluble polysaccharides derived from cereals. The materials were proposed as a fat replacement in a range of manufactured food products. The Committee was unable to reach a decision on the basis of the data then available and had requested further information on the behaviour of the materials in the gut (see Annual report 1997)<sup>9</sup>.

The Company approached the Committee again in 1998 with the information requested previously and requested an opinion on the substantial equivalence of these materials with

---

*Detailed descriptions of underlined words are contained in the Glossary*

items already present in the diet. The Committee concluded that cereal fractions could not be considered to be substantially equivalent to the starting brans from which they had been derived because they had been isolated from the parent material and so might have a different physiological action. In addition these fractions would replace fat as well as act as a source of fibre and thus their use would be different to other cereal products. The Committee therefore recommended that the materials should undergo a full evaluation under the Novel Food Regulation. In addition, the supporting data would need to include information from a limited human tolerance study to confirm the results of the *in vitro* study already conducted, that consumption of these materials would not result in any adverse gastrointestinal effects. The Committee also sought further information on possible intakes of these materials under the conditions of use proposed, with particular attention to be paid to possible intakes by children.

## 4 Applications made to other member states

### GM radicchio rosso and green hearted chicory

- 4.1 The ACNFP was asked for its opinion on an application made under the Novel Foods Regulation to the Netherlands Competent Authority for approval of *Radicchio rosso* and green hearted chicory, both of which had been genetically modified to make the male plant sterile as part of a hybrid breeding programme. The Committee noted that it had already considered the safety of the GM Radicchio rosso under the previous UK voluntary system and had agreed that further compositional data were required before a final opinion could be reached (see Annual Report 1996)<sup>8</sup>. The UK had therefore objected to a marketing consent for food use being issued for these materials under the EC Deliberate Release Directive (90/220/EEC).

Some further information was received from the company, but the Committee considered that this did not adequately address its concerns about possible unintended secondary effects from the genetic modification on phenotype and composition. In particular, the Committee noted that a marker gene encoding resistance to streptomycin and spectinomycin was included with the construct and that the data available did not conclusively demonstrate that only the desired DNA was transferred into the GM plants and that the marker was absent as was claimed. Furthermore, the company had not provided adequate data to demonstrate that the composition of the GM plants was comparable to that of non-GM varieties, in relation to sesquiterpene lactones, amino acids and biogenic amines. The UK Competent Authority had therefore objected to the marketing of these products on these grounds (see letter to Commission at Annex III). It also noted that the labelling of these products was not addressed in the application or in the opinion expressed by the Dutch Competent Authority.

### *Stevia rebaudiana* Bertoni

- 4.2 The ACNFP was asked to consider an opinion from the Belgian Competent Authority that *Stevia rebaudiana* Bertoni, a perennial shrub native to certain regions of South America, should not be approved as a novel food on the basis that the applicant had failed to provide adequate information. The ACNFP agreed with the concerns expressed by the Belgian Competent Authority. It noted particularly that there was a lack of information on estimates of likely intake of the material and that the specification of the material was inadequate, particularly in terms of the level of the active component, stevioside, present. In addition, there was a lack of information on the extent of the metabolism of stevioside by the human gut bacteria and on the possible toxicological consequences of such metabolism. The ACNFP also noted that other expert committees (the EC Scientific Committee for Food and the WHO/FAO Joint Expert Committee on Food Additives) who had reviewed the safety of stevioside, had not been satisfied with the toxicological data available. The views of the UK Competent Authority were forwarded to the Commission (see letter in Annex IV).



## Phospholipids from egg yolk

- 4.3 The ACNFP was asked to consider an initial opinion from the Belgian Competent Authority that phospholipids were acceptable for use in foods where they had been obtained from egg yolk by physical processing, although not following subsequent enzymic processing. The Committee was of the view that the specification of the product was not sufficiently detailed, particularly in terms of the level of protein remaining in the processed product. The dossier also contained inadequate nutritional and toxicological information, especially in regard to the structural similarity of the phospholipids with those in the existing diet, and to bioavailability. The views of the UK Competent Authority were forwarded to the Commission (see letter in Appendix V).

## 5 Other issues considered by the ACNFP

### Potential applications

#### 5.1 (i) Camelina Oil

The ACNFP considered an enquiry from John K King & Sons Limited about obtaining food approval for oil from the plant *Camelina sativa*. This is a member of the Cruciferae family and is being developed as an oilseed crop with food and technical applications. Camelina oil is intended for use in margarine and as a cooking oil.

Initially it seemed likely that Camelina oil would fall within the scope of the Novel Foods Regulation. However, in May 1998, Camelina oil had received approval in France for its use in food on the basis that it was not novel and was considered to meet edible quality standards. Further information also provided evidence of its production in Europe for edible and technical applications from the early twentieth century, up until the 1950s, when its use was largely superseded by rapeseed.

The Committee concluded that Camelina oil could not be defined as a novel food under the EC Novel Foods Regulation as it clearly has a history of food use within the EU. The oil also has a similar composition to other oils (such as borage oil) currently on the market. However, the Committee noted that use of Camelina oil would be subject to the provisions of the UK Food Safety Act 1990 (as amended)<sup>12</sup>. A letter was sent to the Commission, copied to the company, informing them of the opinion of the UK Competent Authority (see letter in Appendix VI).

#### (ii) FRUITRIM®

The ACNFP considered information about FRUITRIM® provided by HAX Ltd. concerning the legality of its use as a food ingredient. This is a mixture of concentrated fruit juice and hydrolysed starch for use as a fat replacer. It has already been marketed in Italy and the USA where it is currently being used in a variety of foods and baked items as a replacement for solid and liquid fats. FRUITRIM® is formed in a patented process which involves a reduction in the water content of the ingredients.

As for another fat replacer, which was considered in 1989 (see 1989 Annual Report)<sup>1</sup>, the Committee concluded that FRUITRIM® is not novel since it is made from conventional food ingredients which can be obtained from commercial sources. A letter was sent to the company, copied to the Commission, advising them of the opinion of the UK Competent Authority (see letter in Appendix VII).

### Reports and other issues

#### 5.2 (i) Statistically valid data to support safety clearance of crop products under the Novel Foods Regulation

The Committee prepared a paper on the statistically valid data necessary to support applications for safety clearance of applications under the EC Novel Foods Regulation. The Committee viewed the paper as a useful way to stimulate debate on this issue with the aim of helping to achieve greater harmonisation in the consideration of applications under the Novel Food Regulation and internationally.

The Committee considered that there were a number of requirements that should be insisted upon. In general, data needed to be gathered over 2 years and from a minimum of 6 sites and should be able to show a statistical significance of 95%. A variety of growing sites should be used in order to take into account the variability of growing conditions across the EU. In some cases a higher number of samples might be needed due to the variability in composition within species. Replicates within each trial site were also required.

The paper was forwarded to the European Commission for discussion. A copy can be found in Appendix VIII.

**(ii) Toxicological assessment of novel foods**

The Committee published a paper on the role of toxicological studies in assessing the safety of GM foods. The Committee considered that long term feeding studies should be carried out where it is relevant and appropriate to do so. However, each case needed to be considered on its merits as complicating factors, in the design and interpretation of such 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. A copy of this paper can be found at Appendix IX.

**(iii) Letter from Chief Medical Officer concerning novel foods for infants**

The Chief Medical Officer (CMO) wrote to the Chairman of the ACNFP seeking advice on whether foods or food ingredients which had been used in adult foods needed to be evaluated under the Novel Foods Regulation before they could be given to the newborn infant. The ACNFP discussed this matter at its March meeting and referred the matter to the European Commission. The Commission advised that the appropriateness of such foods should be considered under the EC Infant Formulae and Follow-on Formulae Directives<sup>13</sup>. This advice was conveyed to the CMO. However, it is unclear whether the scope of these Directives covers the issues addressed and the legal position is being clarified.

**(iv) Joint ACNFP/COMA ad hoc working group meeting on the dietary implications of cumulative nutritional changes in individual novel and conventional foods**

A joint ACNFP/COMA ad hoc Working Group meeting on the implications of cumulative nutritional changes to the diet was held on 10 September 1998. The group discussed recent trends and possible future developments in food manufacturing and processing of novel and conventional foods, and the dietary and health implications that these raised. It focused particularly on how future trends might be monitored. A copy of the minutes of this meeting can be found at Appendix X.

**(v) Risk Assessment: the role of advisory committees**

The Committee was informed that Ministers from the Ministry of Agriculture, Fisheries and Food and the Department of Health were considering whether any changes needed to be made to the overall framework for risk analysis across the food area and how policy decisions were made. As part of this process, they had asked each of the advisory committees to consider how its discussions and advice fitted into this framework and to suggest any improvements which could be made to the current system.

The Committee agreed a number of points. These included the importance of drawing a distinction between the risk assessment and risk management parts of the assessment

process; the importance of increasing public understanding of the concept of risk assessment; and the need for better risk communication about food issues generally, and novel foods particularly.

**(vi) MAFF research & development report on gene transfer**

The Committee was presented with, for information, the results of recently completed research into gene transfer between modified bacteria and resident microflora of the human gut, which had been commissioned by MAFF as part of its programme of work to support the ACNFP's activities.

Copies of the report are available from the MAFF Library, Nobel House, 17 Smith Square, London, SW1P 3JR. This report is a priced publication.

**(vii) Royal Society statement on GM plants for food use**

The Royal Society statement on GM plants for food use was presented to the Committee for information. The Committee considered that this statement made an important contribution to the understanding of the issues raised by GM plants and foods and noted that it highlighted the importance of many of the factors that were already taken into account by the Committee in its assessment of novel foods.

**(viii) Rowett Institute GM potatoes**

Press speculation in 1998 suggested that adverse effects on rats alleged to have been observed in some safety studies conducted at the Rowett Institute on an experimental potato had far reaching implications for the safety of GM foods. The conclusions that had been drawn about these studies were however subsequently called into question. The work was audited under the terms of the ethical Code of Practice of the Medical Research Council. The audit report concluded that the claims which had been made could not be substantiated by the available evidence. The ACNFP was presented with the audit report for information. Due to further speculation about this study, the ACNFP wrote to one of the scientists involved requesting access to additional data that it was claimed were not available to the audit team so that its significance could be considered. The Royal Societies of London and Edinburgh also reviewed the results of this study.

*Reports on the conclusions of the ACNFP and the Royal Society were published in May 1999 and are available from the ACNFP Secretariat (see page 17).*

**(ix) US Food and Drugs Administration (FDA) paper on antibiotic resistance marker genes (ARMs) in transgenic plants**

The Committee was asked for its views on a draft paper produced by the US FDA: 'Guidance for Industry: Use of Antibiotic Resistance Marker Genes in Transgenic Plants'. The Committee felt that the paper was well presented and would be of interest to the educated lay reader as well as to the scientific community. Several Committee members made detailed scientific comments highlighting areas where they felt the consideration of the issues was too narrow or absent. These drew on the Committee's view in its two reports on the use of antibiotic resistance markers (copies available from the ACNFP Secretariat) and took into account work carried out since then, citing a number of pertinent references. The Comments were forwarded to the US FSA by the Secretariat. A copy of the letter can be found at Appendix XI.

**(x) Joint ACNFP/Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) Seminar**

The 1997 Annual Report<sup>9</sup> recorded that the ACNFP was planning to hold a joint discussion meeting with the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment.

This meeting was held in February 1998 and discussed the safety assessment of novel foods for which no conventional counterparts existed and, in particular, looked at the role of animal studies in comparison with human studies in the safety assessment process. The meeting noted the importance of considering the choice of animal species to be used where such a study was considered appropriate. It also considered other aspects of the design of studies.

This meeting was written up and published in the scientific press (Food Additives and Contaminants, 1999, Vol 16 (1) p37-45).

**(xi) ACNFP consideration of Greenpeace reports**

The ACNFP considered two documents submitted to it by Greenpeace, and published responses to both of these. The response to the Greenpeace critique of the safety assessment of GM soya, at Appendix XII and the response to the Greenpeace report 'Genetic Engineering: too good to go wrong?' can be found at Appendix XIII.

**(xii) Other papers for information**

The ACNFP were also presented with: a copy of a paper from Dr Mae Wan Ho on gene technology and gene ecology of infectious diseases and one from the US FDA on the safety assurance of foods derived from modern technology.

## 6 Other activities

### Improving the transparency of the ACNFP

- 6.1 In 1997, the ACNFP agreed a number of ways to increase the transparency of its safety assessment process. The Committee agreed that it would continue to inform the public of meetings by the publication of the agenda in a pre-meeting News Release. In addition, the Committee decided that from March 1998, publication of the minutes of its meetings, along with the Secretariat papers presented at the meeting (from May 1998), was the most appropriate way to inform the public about the proceedings. These are available on the MAFF website (<http://www.maff.gov.uk>) or from the ACNFP Secretariat. If any points of substance are raised by the public or interested parties on particular items after the meeting, these could then be considered at the next meeting, or by post if appropriate.

The ACNFP has continued to publish reports on its evaluations once the assessment procedures have been completed. Commission decisions on the authorisation of novel foods under the Novel Foods Regulation (see Section 1), which are based on the opinions of ACNFP and other EC Competent Authorities (or the Standing Committee for Foodstuffs) will be published in the Official Journal of the European Communities. The ACNFP will continue to encourage companies which make applications through the UK Competent Authority to deposit the accompanying dossier in the British Library. The Committee has also published a brochure, which outlines the work of the Committee and its members.

The Committee had also agreed that it would hold open meetings whenever possible and especially on generic topics of particular public interest. An ACNFP subgroup that examined the feasibility of the post market monitoring of novel foods, held two meetings in 1998 which were open to invited observers (see Section 6.2 below).

Finally, the Committee agreed to consider further measures in 1999 for increasing the involvement of the public and others in its work.

### ACNFP sub-group on the post-market monitoring of novel foods

- 6.2 In order to increase public confidence in novel foods, including those that had ingredients derived from GM crops, and demonstrate that the Government was responding to consumer concerns, a subgroup of the ACNFP was set up to look at the practicality of the post market monitoring of novel foods.

This ACNFP sub group, which included relevant ACNFP members, epidemiologists and representatives from major supermarkets, met twice in 1998 (March 16 and December 10) to discuss this issue. Invited observers from various organisations, including Greenpeace and the Consumers Association, also attended the meetings. The minutes of these meetings have been published and are available on the MAFF website or from the ACNFP Secretariat (see page 17). The discussions on this issue are continuing.

# 7 Developments elsewhere

## European Commission proposal for a directive on food irradiation

- 7.1 A Common Position for a Directive concerning foods and food ingredients treated with ionising radiation was formally adopted at the Internal Market Council (IMC) on 27 October 1997. During the European Parliament's second reading, a number of amendments were proposed. Council agreed some of these amendments and the remainder were the subject of conciliation procedures. Council and the European Parliament agreed the final text in January 1999. All Member States are required to implement the Directives by 20 September 2000.

The Directive has two parts; the Framework Directive and the Implementing Directive. The Framework Directive lays down general provisions such as the conditions for treatment, the rules governing the approval and control of irradiation facilities and labelling. The Implementing Directive will establish an initial positive list of foodstuffs which could be treated with ionising radiation and freely traded across the whole Community; at present this only contains dried aromatic herbs, spices and vegetable seasoning. The provisions of the Directive are broadly in line with the current UK legislation and, once implemented, will harmonise controls across the EU.

Further details can be obtained from the MAFF Secretary (see page 17).

## Labelling of GM foods

- 7.2 The European Commission announced in 1997 that it intended to introduce a more coherent approach to the labelling of GM foods throughout the food chain. As a first step, the Commission sought agreement on detailed rules for the labelling of ingredients obtained from GM soya and maize that had been approved for marketing before the Novel Foods Regulation came into force. This was to ensure that the labelling applicable to such products is in line with that for products considered under the Novel Foods Regulation. Member States at the Agriculture Council finally agreed these rules, with a number of UK Presidency amendments incorporated, on 26 May 1998. EC Regulation (1139/98)<sup>14</sup> concerning the labelling of GM soya and maize came into force simultaneously in all Member States on 1 September 1998. The Regulation sets a precedent for the labelling of all GM foods sold in the EU.

Member States were required to make domestic legislation giving powers of enforcement for the Soya and Maize Labelling Regulation (1139/98). To ensure that the GB Regulations were practicable, two consultations were held between July 1998 and February 1999. The Food Labelling (Amendment) Regulations 1999<sup>15</sup> subsequently came into force on 19 March 1999. These new measures mean that outlets selling foods containing GM soya and maize that are not properly labelled may be prosecuted and fined up to £5,000. The controls will also apply to UK restaurants, cafes, bakers and delicatessens from 19 September 1999. The UK is the first Member State to require information on GM foods to be provided in such establishments.

Proposals are awaited from the European Commission for a negative list of products that would not require labelling because processing techniques used to produce the food ingredients had resulted in the removal or destruction of the DNA and protein arising from

its modification; and a threshold to allow for low levels of adventitious contamination where all reasonable efforts have been made to obtain non-GM material.

Further details can be obtained from the MAFF Secretary (see page 17).



## 8 Contact points

For further information about the general work of the Committee or about specific scientific points concerning individual submissions (which have been made or are being made) contact in the first instance:

Mr Nick Tomlinson  
Ministry of Agriculture, Fisheries and Food  
Joint Food Safety and Standards Group  
Room 235  
Ergon House  
c/o Nobel House  
17 Smith Square  
London SW1P 3JR

Information about health or toxicological matters may be obtained by contacting, in the first instance,

Mrs Sue Hattersley  
Department of Health  
Joint Food Safety and Standards Group  
Room 653C  
Skipton House  
80 London Road  
London SE1 6LW

The MAFF Website can be found at <http://www.maff.gov.uk>

Information can also be requested via e-mail at: [a.acnfp@jfssg.maff.gov.uk](mailto:a.acnfp@jfssg.maff.gov.uk)

## 9 References

1. Advisory Committee on Novel Foods and Processes. *Annual Report 1989*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1990. (Available from the ACNFP Secretariat).
2. Advisory Committee on Novel Foods and Processes. *Annual Report 1990*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1991. (Available from the ACNFP Secretariat).
3. Advisory Committee on Novel Foods and Processes. *Annual Report 1991*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1992. (Available from the ACNFP Secretariat).
4. Advisory Committee on Novel Foods and Processes. *Annual Report 1992*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1993. (Available from the ACNFP Secretariat).
5. Advisory Committee on Novel Foods and Processes. *Annual Report 1993*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1994. (Available from the ACNFP Secretariat).
6. Advisory Committee on Novel Foods and Processes. *Annual Report 1994*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1995. (Available from the ACNFP Secretariat).
7. Advisory Committee on Novel Foods and Processes. *Annual Report 1995*. Department of Health and Ministry of Agriculture, Fisheries and Food, 1996. (Available from the ACNFP Secretariat).
8. Advisory Committee on Novel Foods and Processes. *Annual Report 1996*. Department of Health and Ministry of Agriculture, Fisheries and Food 1997. (Available from the ACNFP Secretariat).
9. Advisory Committee on Novel Foods and Processes. *Annual Report 1997*. Department of Health and Ministry of Agriculture, Fisheries and Food 1998 (Available from the ACNFP Secretariat).
10. European Commission. Regulation (EC) No 258/97 of the European Parliament and of the Council concerning novel food and novel food ingredients. *Official Journal of the European Communities*, No L43 of 14 February 1997.
11. Commission of the European Communities 1997: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No. 258/97 of the European Parliament and of the Council. C(97) 2634 final. *Official Journal of the European Communities* Vol. 40 L253/1-45 16 September 1997.
12. UK Food Safety Act (1990). ISBN No. 0 –10-541690-8.
13. Commission Directive (EC) No. 4/96 on Infant Formulae and Follow-on Formulae. *Official Journal of the European Communities*, L49, 28 February 1996.

14. Council Regulation (EC) No 1139/98 concerning the compulsory indication of the labelling of certain foodstuffs produced from genetically modified organisms of particulars other than those provided for in Directive 79/112/EEC. *Official Journal of the European Communities*, L159/4-7, 3 June 1998.
15. SI 1999 No. 747. The Food Labelling (Amendment) Regulations 1999.

# 10 Glossary

***Agrobacterium tumefaciens* mediated transformation:** a system of genetic modification which uses the bacterium *Agrobacterium tumefaciens*, that causes crown gall disease, to introduce DNA into plant tissues.

**binary transformation vector:** two autonomous replicating plasmids, with the genes to be transferred on one plasmid and genes encoding the necessary function for transfer on the second plasmid.

**co-factor:** a substance, such as a co-enzyme (for example, ATP) with which another molecule must unite in order to function or to become active.

**downregulation:** downregulation of a gene leads to a reduction in the amount of protein encoded by that gene.

**effect gene:** a gene or gene fragment specifically introduced to have a particular effect e.g. polygalacturonase.

**expression cassette:** a discrete fragment of DNA in which a gene of interest is physically attached to regulatory sequences sufficient to result, in an appropriate background, in its expression.

**germplasm:** the genetic variability, represented by germ cells or seeds, available in a particular species of plants.

**glycoalkaloids:** natural toxins found in certain species that confer protection against predation.

**inbred:** plant that has been self-pollinated over several generations and is nearly genetically uniform.

**insert:** DNA transferred to a plant cell during transformation.

**linters:** Short fibres removed from cotton seeds after ginning.

**multiple cloning site:** a short synthetic sequence of DNA containing contiguous/overlapping sites for restriction endonucleases to facilitate cloning into vectors.

**promoter:** key control element that enables a gene to be transcribed into mRNA.

**‘sense’:** insertion of a gene, by genetic modification, in the same orientation as an endogenous gene.

**selectable marker (gene):** gene with a phenotype that can be selected for in gene transfer experiments. Selectable marker genes are used to enable the selection/detection of neighbouring sequences in a gene construct.

**selfed:** a plant that has been pollinated with its own pollen.

**single cross hybrids:** hybrids produced from the crossing of the GM parent line with the non-GM parent line.

**Southern hybridisation:** a technique that uses probes consisting of complementary single-stranded nucleic acid to detect the presence of specific sequences of DNA that have been isolated from an organism.

**terminator:** DNA sequence that terminates the synthesis of mRNA.

**trait:** an observable characteristic.

**truncated PG gene:** part of the PG gene (i.e. 731 base pair fragment) which has been constructed *in vitro*.

# Appendix I

## ACNFP – remit, membership and list of members’ interests, code of conduct and interactions with other committees

### Remit

The Advisory Committee on Novel Foods and Processes is an independent body of experts whose remit is:

“to advise Health and Agriculture Ministers of Great Britain and the Heads of the Departments of Health and Social Services and Agriculture for Northern Ireland on any matters relating to the irradiation of food or to the manufacture of novel foods or foods produced by novel processes having regard where appropriate to the views of relevant expert bodies”.

The Secretariat is provided jointly by officials of the Department of Health and the Ministry of Agriculture, Fisheries and Food. As well as formal meetings, the Committee organises workshops on specific topics related to its remit.

The interaction between the ACNFP and other independent advisory committees is outlined in Figure 1 on page 33.

### Membership and Members’ Interests

The membership of the Committee provides a wide range of expertise in fields of relevance in the assessment of novel foods and processes. A list of the membership during 1998, together with the names of assessors and the secretariat may be found overleaf.

In common with other independent advisory committees the ACNFP is publishing a list of its members’ commercial interests. These have been divided into different categories relating to the type of interest:-

- |               |                                                                                                |
|---------------|------------------------------------------------------------------------------------------------|
| Personal:     | a) direct employment or consultancy;<br>b) occasional commissions;<br>c) share holdings.       |
| Non-personal: | a) fellowships;<br>b) support which does not benefit the member directly<br>e.g. studentships. |

Details of the interests held by members during 1998 can be found on pages (25)

A copy of the code of conduct for ACNFP members can be found on pages (28)

## Membership of the committee during 1998

### Chairman

Professor Janet Bainbridge, BSc, PhD, GradCertEd (Tech), MiBiol, CBiol, SOFHT  
School of Science and Technology  
University of Teesside, Middlesbrough (from September 1997)

### Members

Professor P J Aggett, MSc, MB, ChB, FRCP (Lond, Edin & Glasg), DCH  
Head of Lancashire Postgraduate School of Medicine and Health

Professor C M Brown, BSc, PhD, DSc, CBiol, FIBiol, FIBrew, FRSE  
Vice Principle, Heriot-Watt University Edinburgh (from September 1997)

Dr P Dale BSc PhD, CBiol, MIBiol  
Research Group Leader, Genetic Modification and Biosafety Assessment,  
John Innes Centre, Norwich  
Honorary Reader of the University of East Anglia

Dr M J Gasson, BSc, PhD  
Head, Department of Genetics and Microbiology  
Institute of Food Research, Norwich

Dr J Heritage, BA, D.Phil, C.Biol, MIBiol  
Division of Microbiology  
School of Biochemistry and Molecular Biology  
University of Leeds

Professor D A Ledward, MSc, PhD, FIFST  
Professor of Food Science  
University of Reading

Reverend Dr M Reiss BSc, MA, PhD, FIBiol  
Senior Lecturer, Homerton College, University of Cambridge

Mrs E Russell BSc  
Consumer Representative

Professor I Rowland, BSc, PhD  
Director, Northern Ireland Centre for Diet and Health  
University of Ulster, Coleraine

Professor T Sanders, BSc, PhD, DSc  
Head of Department of Nutrition and Dietetics  
Kings College, London

Professor H Sewell MB ChB, BDS, MSc, PhD, FRCP (Lond & Glas), FRCPATH, FMedSci  
Head of Immunology, Faculty of Medicine and Health Science, University Hospital Medical  
School, Nottingham.

Dr N A Simmons FRC Path, FIFST  
Emeritus Consultant in Microbiology  
Guy's & St Thomas' Hospital Trust London

Dr K Venables MD FRCP FFOM MFPHM (retired from the Committee in October 1998)  
Senior Lecturer in Epidemiology, National Heart and Lung Institute, Imperial College of Medicine, London

Professor R Walker PhD, CChem, FRSC, FIFST  
Professor of Food Science, University of Surrey

Professor H F Woods BSc, BM BCh, DPhil, Hon.FFOM, FIFST, FFPM, FRCP(Lond & Edin)  
Sir George Franklin Professor of Medicine, Division of Molecular and Genetic Medicine  
University of Sheffield

### Assessors

Dr J Bell	Ministry of Agriculture, Fisheries and Food
Dr A Wadge	Department of Health
Dr I Lawrence	Department of Trade and Industry
Dr J Furlong	Health and Safety Executive
Dr P Burrows	Department of the Environment, Transport and the Regions
Professor A Gilmour	Department of Agriculture, Northern Ireland
Mr I Jackson	Welsh Office
Ms M McAllen	Scottish Office, Agriculture and Fisheries Department

Member	Personal Interest		Non-Personal Interest		Partner Interest
	Company	Interest	Company	Interest	
Professor J Bainbridge (CHAIRMAN)	None		Various	Departmental commissioned research and student placements	None
Dr M J Gasson (DEPUTY CHAIRMAN)	None		Various	Departmental commissioned research	None
Professor P J Aggett	Nestec, Wyeth, Borax	Ad hoc consultancy Ad hoc consultancy	Nestec, FDF, Abbot, Unilever, Meat & Livestock Commission	Departmental commissioned research and consultancies	None
Professor C M Brown	None	None	None	None	None



	Personal Interest		Non-Personal Interest		Partner Interest
Dr P Dale	None		European Commission DGXI United Nations Industrial Development Organisation DETR Two MAFF contracts – Seeds Property purchaser	Consultant to EC DGXI  Consultant to UNIDO Call off consultant  Call-off consultant Advisor on GM biosafety	None
Dr J Heritage	None	None	None	None	None
Professor D A Ledward	None		Various	Departmental teaching & research funded by various food companies	None
Revd Dr M Reiss	None	None	None	None	None
Professor I Rowland	CNI Unilever Yakult UK	Consultancy Consultancy Consultancy lapsed	Coulter Food Science Kellogg's Coca-Cola St Ivel Orafti Biscuit cake Chocolate & Confectionary Alliance (BCCA) Medici Pharmaceuticals (Germany) Kirin (Japan)	Consultancy  Research Research Research Research  Research lapsed  Research lapsed Consultancy lapsed	None
Mrs E Russell	The Boots Company PLC	Shareholder	None	None	Husband board member of The Boots Company plc.
Professor T Sanders	Nutrasweet Seven Seas Limited ILSI Europe	Consultancy Consultancy  Fee	Unilever   Cultor Food Science	Free supply of oils & fats for research purposes Research grant	None
Professor H Sewell	None	None	None	None	None

	Personal Interest	Non-Personal Interest	Partner Interest
Dr N Simmons	Food Micro Limited Infection Management Ltd Marks & Spencer plc McDonalds Restaurants Ltd PPP/ Columbia Healthcare Ltd Waitrose Ltd Worshipful Company of Fishmongers	Director & Shareholder Advisor & Shareholder Independent advisor Independent advisor Consultant Independent advisor Bacteriologist	None
Dr K Venables	None	None	None
Professor R Walker	Coffee Science Inf. Centre Colloids Naturel International Nestec Borex Europe Ltd Holland Sweetners Xyrofin Sucralose Hoffman-La-Roche Tate and Lyle Specialty Sweetners Cadbury Beverages Proctor & Gamble IDV Ltd Food Safety Advisory Centre Coffee News Information Service RHM	Consultancy Consultancy Fee Consultancy Fee Fee Fee Fee Consultancy lapsed Consultancy lapsed Consultancy lapsed Consultancy lapsed Consultancy lapsed Consultancy lapsed	Nestle Ltd Research lapsed None

	Personal Interest		Non-Personal Interest		Partner Interest
Professor H F Woods	None	None	Wide range of national and international food and chemical companies	Dean of the University of Sheffield Faculty of Medicine which has extensive activity in teaching and research in nutrition and toxicology and in topics related to and supported by, many companies in the food and chemical industry  Trustee of the Harry Botton Charitable Trust and Special Trustees for the former United Sheffield Hospitals	None

## Register of interests: a code of conduct for members of the Advisory Committee on Novel Foods and Processes

### Introduction

1. This code of conduct guides members of the Advisory Committee on Novel Foods and Processes as to the circumstances in which they should declare an interest in the food industry.
2. The advice of the ACNFP concerns matters which are connected with the food industry and it is therefore desirable that its members and those of its support groups should have a good understanding of the work of the industry. It is also desirable that some members should have practical experience of the scientific problems of product development and safety evaluation. The food industry relies heavily on the advice of a wide range of specialists including scientists outside the industry in, for example, the universities. To avoid any public concern that commercial interests might affect the advice of the Committee, Ministers have decided that the arrangements which govern relationships between members and the food industry and information on significant and relevant interests should be on public record.

### Definitions

3. In this code, 'food industry' means:
  - (i) companies, partnerships or individuals who are involved with the production, manufacture, packaging, sale or supply of food or food processes, subject to the Food Safety Act 1990;
  - (ii) trade associations representing companies involved with some products;

- (iii) companies, partnerships or individuals who are directly concerned with research, development or marketing of a food product which is being considered by the ACNFP.
4. In this code 'the Secretariat' means the Secretariat of the ACNFP.

### Different types of interest

5. The following is intended as a guide to the kinds of interests which should be declared. Where a member is uncertain as to whether an interest should be declared they should seek guidance from the Committee's Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chairman at that meeting. **If a member has an interest not specified in these notes but which they believe could be regarded as influencing their advice, they should declare it.** However, neither the members nor the Secretariat are under any obligation to search out links between one company and another, for example where a company with which the member is connected has an interest in a food industry company of which the member is not aware and could not reasonably be expected to be aware.

### Personal Interests

6. A personal interest involves payment to the member personally. The main examples are:-
- (i) *Consultancies*: any consultancy, directorship, position in or work for the food industry which attracts regular or occasional payments in cash or kind.
  - (ii) *Fee-Paid Work*: any work commissioned by the food industry for which the member is paid in cash or kind.
  - (iii) *Share holdings*: any share holding in or other beneficial interest in shares of the food industry. This does not include share holdings through unit trusts or similar arrangements where the member has no influence on financial management.

### Non-Personal Interests

7. A non-personal interest involves payment which benefits an organisation or department for which a member is responsible, but is not received by the member personally. The main examples are:-
- (i) *Fellowships*: the holding of a fellowship endowed by the food industry.
  - (ii) *Support by the Food Industry*: any payment, other support or sponsorship by the food industry which does not convey any pecuniary or material benefit to a member personally but which does benefit their position or department, e.g.
    - a) a grant from a company for the running of a unit or department for which a member is responsible;
    - b) a grant or fellowship or other payment to sponsor a post or a member of staff in the unit for which a member is responsible. This does not include financial assistance for students;
    - c) the commissioning of research or other work by, or advice from, staff who work in a unit for which a member is responsible.

Members are under no obligation to seek out knowledge of work done for or on behalf of the food industry by departments for which they are responsible, if they would not normally expect to be informed. Where members are responsible for organisations which receive funds from a very large number of companies involved in the food industry, the Secretariat can agree with them a summary of non-personal interests rather than draw up a long list of companies.

- (iii) *Trusteeships*: any investment in the food industry held by a charity for which an ACNFP member is a trustee.

Where a member is a trustee of a charity with investments in the food industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

### Contractual obligations of confidentiality

8. Some members of the Committee may, **at the time of adoption of this Code** or (in the case of new members) on their joining the Committee, be bound by the terms of a contract which requires them to keep the fact of the contractual arrangement confidential. As a transitional measure any member so affected shall seek to agree an entry for the public register with the other party. If such agreement does not prove possible, the member shall seek a waiver permitting them to disclose their interest, in confidence, to the Chairman and the Secretariat. The Secretariat will maintain a confidential register of such disclosures which will not form part of the public record.
9. On adoption of this Code members shall not enter into new contractual obligations which would inhibit their ability to declare a relevant interest.

### Declaration of interests to the Secretariat

10. Members of the Committee, should inform the Secretariat **in writing** when they are appointed of their **current personal and non-personal** interests, including the principal position held. Only the name of the company and the nature of the interest is required, the amount of any salary, fees, sharing holding etc. need not be disclosed to the Secretariat. An interest is current if the member has an on-going financial involvement with the food industry e.g. if they hold shares in a food company, if they are in the consultancy contract with the food industry, or if they are in the process of carrying out work for the food industry. Members are asked to inform the Secretariat at the time of any change of their **personal** interest, and will be invited to complete a declaration form once a year. It would be sufficient if changes in non-personal interests are reported in the annual declaration form following the change. (Non-personal interests involving less than £1,000 from a particular company in the previous year need not be declared to the Secretariat).

### Special position of the Chairman

11. It is not appropriate for the Chairman of the Advisory Committee on Novel Foods and Processes to have any current personal interest in the food industry.

### Declaration of interests at meetings and participation by members

12. Members are required to declare relevant interests at Committee meetings, and to state whether they are personal or non-personal interests and whether they are specific to the product under consideration or non-specific:

- (i) A member must declare a **personal specific** interest if they have **at any time** worked on the product or process under consideration and have personally received payment for that work, in any form, from the food industry. The member shall take no part in the proceedings as they relate to the product or process, except that they may at the Chairman's discretion answer questions from other members. If the interest is no longer current, the member should declare it as a **lapsed personal specific** interest;
  - (ii) A member must declare a **personal non-specific interest** if they have a **current** personal interest in the food company concerned which does not relate specifically to the product under discussion. The member shall take no part in the proceedings as they relate to the product, except that they may at the Chairman's discretion answer questions from other members;
  - (iii) A member must declare a **non-personal specific interest** if they are aware that the department for which they are responsible has at any time worked on the product or process but the member has not personally received payment in any form from the food industry for the work done. The member may take part in the proceedings unless they have personal knowledge of the product or process through their own work or through direct supervision of other people's work, in which case they should declare this and not take part in the proceedings (except to answer questions);
  - (iv) There is no need for members to declare **non-personal non-specific** interests (i.e. if a member is aware that the department for which is responsible is currently receiving payment from the food industry company concerned which does not relate specifically to the product or process under discussion). If, exceptionally, a member feels such an interest might be thought to influence his advice, they should seek guidance from the Chairman on whether to draw the facts to the attention of other members.
13. The examples, of 'personal', 'non-personal' and 'current' interests given in the previous paragraphs should be read in the context of paragraphs 6, 7 and 10. 'Taking part in the proceedings' includes both speaking and, if necessary, voting. A member who is in any doubt as to whether they has an interest which should be declared, or whether they should take part in the proceedings, should ask the Chairman for guidance. The Chairman has the power to determine whether or not a member with an interest shall take part in the proceedings.
14. If a member is aware that a product or process under consideration is or may become a competitor of a product or process manufactured, sold or supplied by a company in which the member has a **current personal** interest, they should declare his interest in the company marketing the rival product or process. The member should seek the Chairman's guidance on whether they should take part in the proceedings.

### Register of interests

15. A record is kept by the Secretariat of:
- (i) names of members who have declared interests to the Secretariat on appointment, when an interest first arises or through the annual declaration, and the nature of the interest;

- (ii) names of members who have declared interests at meetings of the Committee, giving dates, names of relevant products and companies, details of the interest declared and whether the member took part in the proceedings.

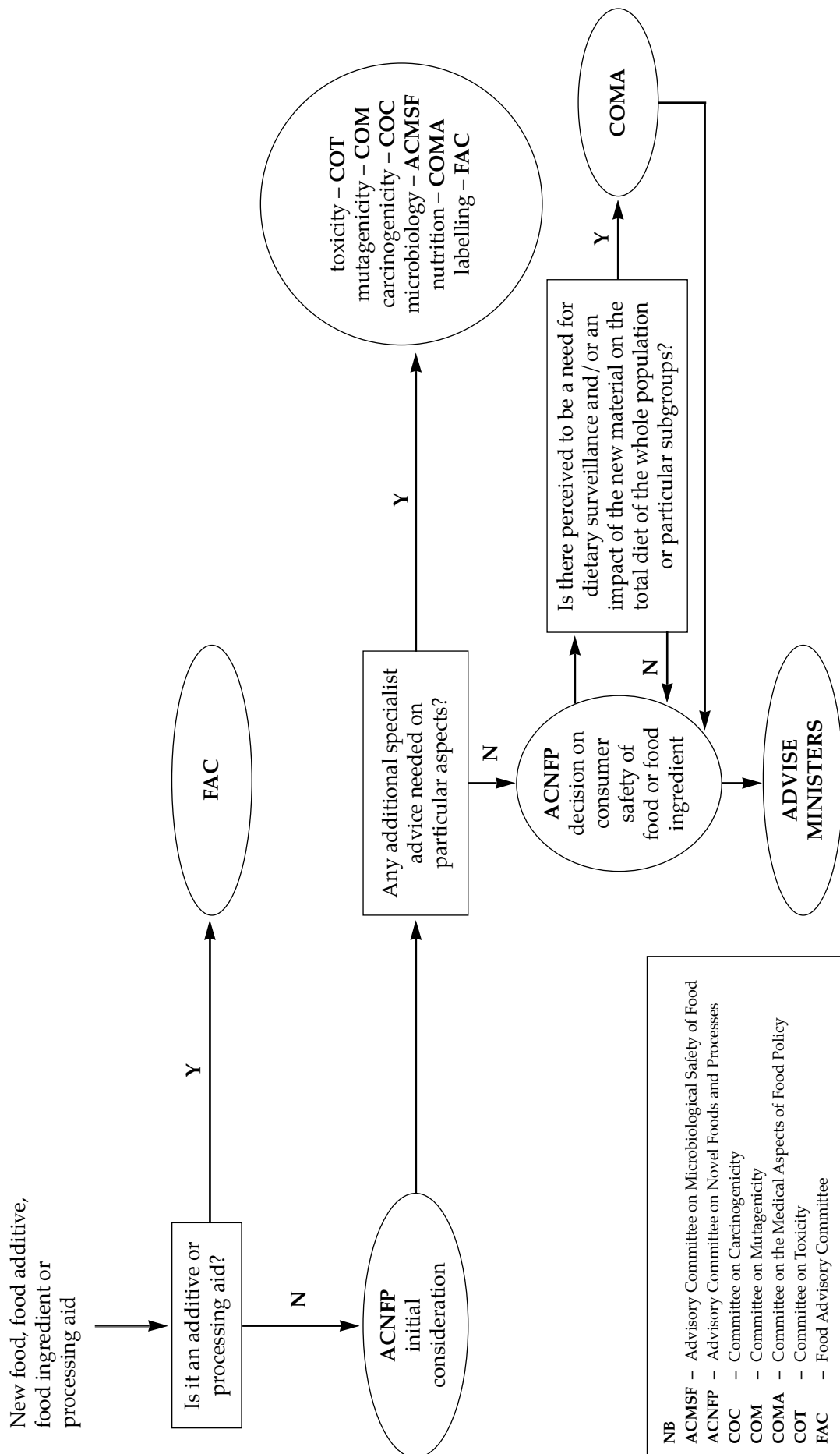
### Publication

16. Information about interests declared by members to the Secretariat will be published each year in the Annual Report of the ACNFP.

#### ***Revised Code of Conduct for Members of the ACNFP***

*In early 1999 the ACNFP agreed a new code of conduct in accordance with the guidelines issued by the Cabinet Office following the Nolan Report on Standards in Public Life. The revised code of conduct is published on the ACNFP website (<http://www.maff.gov.uk/food/novel/acnfp.htm>) and is available on request from the ACNFP Secretariat (see page 17).*

**Figure 1: Relationship of ACNFP with other expert committees involved in the assessment of food safety.**





# Appendix II

## UK Competent Authority initial assessment report on the safety assessment of processed products from genetically modified tomatoes derived from line TGT7F: final report sent to the European Commission

### Introduction

1. In March 1998, the Advisory Committee on Novel Foods and Processes (ACNFP) received an application from Zeneca Plant Science for a safety evaluation of the processed products from genetically modified (GM) processing tomatoes (*Lycopersicon esculentum* Mill.) derived from line TGT7F. The tomatoes have been genetically modified to improve the processing quality by reducing the levels of the naturally occurring pectin-degrading enzyme polygalacturonase (PG).
2. The GM tomato was genetically modified using Agrobacterium tumefaciens mediated transformation to insert a partial synthetic PG gene from the tomato variety 'Alisa Craig', in the sense orientation, and the introduction of the *nptII* gene originating from *Escherichia coli* (*E. coli*.) as a selectable marker.
3. The ACNFP has already looked at the GM tomatoes and their products under the UK's voluntary system that operated prior to the introduction of EC Regulation 258/97 on Novel Foods and Novel Food Ingredients. Tomato paste produced from the GM tomatoes has been on sale in the UK since February 1996. Nevertheless, not all products approved under the voluntary system have so far been marketed and so it was decided to carry out a full assessment as required by Regulation 258/97. The GM tomatoes fall into category 3.1 of the European Commission's Guidelines on the Assessment of Novel Foods. The Committee's consideration of the data provided is presented according to the information requirements defined in these Guidelines.

### Essential information requirements for a safety assessment under class 3.1 of the European Commission's guidelines

#### I. SPECIFICATION OF THE NOVEL FOOD

4. No specification was provided on products by the company although, copies of all relevant international and EU-agreed standards have been provided. The company has also confirmed that it will also produce products according to the relevant food safety legislation applicable at the time of production, when a product is not specified under a Codex standard or EU legislation.

*Detailed descriptions of underlined words are contained in the Glossary*

## 5. Specification of host plant:

- |    |                        |                                                                                                                                                                        |
|----|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| a. | family name            | <i>Solanaceae</i>                                                                                                                                                      |
| b. | genus                  | <i>Lycopersicon</i>                                                                                                                                                    |
| c. | species                | <i>esculentum</i>                                                                                                                                                      |
| d. | subspecies             | Mill.                                                                                                                                                                  |
| e. | cultivar/breeding line | Hybrids derived from the modified parental inbred line TGT7F. The proposed names for two varieties derived from TGT7F transformation event are: Vegadura and Vegaspeso |
| f. | common name            | Tomato                                                                                                                                                                 |

## Product labelling

6. The products will be labelled according to Article 8 of the Novel Food and Novel Foods Ingredients Regulation 258/97 and any other applicable labelling provisions in Community law. The proposed label on the processed tomato products will follow that already in use voluntarily on the cans of tomato paste on sale in two of the UK's supermarket chains. The proposed labelling is:  
 'produced from genetically modified tomatoes' or  
 'made from genetically modified tomatoes'

## II. EFFECT OF THE PRODUCTION PROCESS APPLIED TO THE NOVEL FOOD

## Production process

7. The processing of tomatoes can be divided into two categories: those intended for products where discrete pieces of tomato are present after processing (whole peeled, diced/chopped tomatoes etc.) and those without discrete pieces after processing (sauces, puree etc).
8. Tomato products in the first categories will require the removal of the skin. The two main commercial methods of skin removal in Europe involve the use of steam/blanching, or infra-red radiation. Temperatures of 90-100°C for a maximum of 60 seconds are used for steam and peeling whereas infra-red peeling involves temperatures in excess of 700°C for up to 20 seconds. The use of caustic soda as a peeling method is prohibited for processing tomatoes in Europe. Newer methods such as wet steam peeling and dry vacuum systems are being developed.
9. After the peeling process, tomatoes to be sold as whole peeled tomato fruit will be sorted by size and packed into containers. Tomatoes to be sold as a diced/chopped product are, chopped as appropriate and packed into containers. Tomato juice or puree is then added to the top of the container along with other ingredients if necessary before closure of the containers and sterilisation by heat.
10. The second category of tomato products, sometimes referred to as comminuted products, undergo a "breaking" step during which the chopped tomatoes are heat treated at temperatures equal to or greater than 65°C for up to 5 minutes followed by tomato material extraction, sieving and pulp concentration. The resulting concentrate forms the basis for sauces, purees and pastes. The end products are packaged appropriately and undergo a final heat processing step to ensure sterilisation. Quantitative data on processing

performance of the GM lines confirmed that the GM fruit displayed improved processing characteristics (the intended effect of genetic modification) over non-GM controls, in terms of thicker paste, increased product yields, and reduction of associated wastes.

### III. HISTORY OF THE ORGANISM USED AS THE SOURCE OF THE NOVEL FOOD

11. The wild *Lycopersicon* genus is native to the Andean region from Columbia to Northern Chile, this region being the centre of origin and diversity. Mexico was probably the source of the cultivated tomato that was introduced into Europe over two centuries ago. No weedy species of tomato are known in Europe.
12. Development of improved tomato varieties by selection from the original germplasm base imported from South America to Europe began when the tomato was recognised as a nutritional and versatile food. The predominant method of generating processing tomato varieties is by the production of single cross hybrids. This method allows the combination of desirable traits from defined inbred parents. The largest producers of tomatoes in the EU are Italy, Greece and Spain.

### IV. EFFECT OF THE GENETIC MODIFICATION ON THE PROPERTIES OF THE HOST ORGANISM

13. The host is the commercial cultivated tomato *L. esculentum* Mill. The modification has been undertaken in the cultivated commercial inbred line TGT7. The transgenic inbred parental line chosen had both reduced PG enzyme activity and agronomic characteristics identical to those of the commercial inbred line TGT7. This transgenic parental line was coded TGT7F.
14. The vector construct, pJR16S, was used for the genetic modification of the commercial inbred line TGT7. The vector construct was based on the binary transformation vector, pBin 19 (Bevan 1984)<sup>3</sup>; this contains an effective selectable marker gene: the neomycin phosphotransferase (*nptII*) gene and a multiple cloning site for the insertion of effect genes. This vector allows the introduction of DNA into the tomato genome using *A. tumefaciens* mediated transformation.
15. The gene expression cassette consisting of a synthetic truncated PG gene in the sense orientation under the control of the Cauliflower Mosaic virus (CaMV) 35S promoter and the nopaline synthase (nos) terminator was inserted into the existing backbone of pBin 19. A few small synthetic linker DNA fragments were also inserted during the construction of the pJR16S vector.
16. Polygalacturonase is an enzyme involved in the breakdown of pectin molecules, and is located in the cell wall of tomato fruits. The enzyme accumulates during ripening. Pectin is a large molecule, consisting mainly of galacturonic acid. The PG enzyme facilitates the cleavage of pectin chains between adjacent galacturonic acid residues. The introduction of the truncated PG gene into tomato plants, has led to the downregulation of the PG function. The result of this downregulation is that the tomato ripens normally but softens less quickly. The *nptII* gene confers resistance to the antibiotics neomycin and kanamycin, by encoding the enzyme aminoglycoside (3') phosphotransferase II (APH(3')II). It was used as a selectable marker gene in the early stages of the development of the GM line allowing the identification of the transformed cells by enabling them to grow in the presence of the antibiotic kanamycin.

Detailed descriptions of underlined words are contained in the Glossary

TABLE I – SUMMARY OF THE DNA SEQUENCES FOUND IN PJR16S:

DNA Sequence Element	Size bp	Function	Origin	References
Left border	25	This border delineates the DNA transferred to plant cells.	<i>A. tumefaciens</i> Ti plasmid	Zambryski <i>et al.</i> , 1980.
Origin of M13 fragment	406	This fragment forms part of a larger region that required for the replication of the M13 in bacteria.	Bacteriophage M13	Wezenbeek <i>et al.</i> , 1980; Yanish-Perron <i>et al.</i> , 1985.
<i>Lac Z</i> gene Fragment	156	This fragment is derived from the lactase operon of <i>E. coli</i> .	<i>E. coli</i> .	Beckwith and Singer, 1966; Bevan, 1984.
CaMV 35S promoter	529	This fragment is responsible for the efficient expression of the PG effect genes (Smith <i>et al.</i> , 1988, 1990).	Cauliflower Mosaic virus	Franck <i>et al.</i> , Odell <i>et al.</i> , 1985.
PG sense	731	The expression of this fragment in sense leads to the downregulation of PG.	Tomato, var. Alisa Craig	Grierson <i>et al.</i> , Smith <i>et al.</i> , 1990.
Nos 3' end	247	This fragment aids the termination of mRNA synthesis.	<i>A. tumefaciens</i> Ti plasmid	Hernalsteens <i>et al.</i> , 1980; Bevan <i>et al.</i> , 1983.
<i>Lac Z</i> gene fragment	231	This fragment is derived from the lactase operon of <i>E. coli</i> .	<i>E. coli</i> .	Beckwith and Singer, 1996; Bevan, 1984.
M13 gene III fragment	440	This fragment is derived from gene III.	Bacteriophage M13	Wezenbeek <i>et al.</i> , 1980; Yanish-Perron <i>et al.</i> , 1985.
Nos 3' end	258	This fragment aids the termination of mRNA synthesis.	<i>A. tumefaciens</i> Ti plasmid	Hernalsteens <i>et al.</i> , 1980; Bevan <i>et al.</i> , 1983.
<i>ocd</i> gene fragment	209	This is a fragment derived from the <i>ocd</i> gene of <i>A. tumefaciens</i> Ti plasmids.	<i>A. tumefaciens</i> Ti plasmid	Sans <i>et al.</i> , 1987, 1988; Schindler <i>et al.</i> , 1989.
<i>nptII</i>	800	This fragment is derived from the transposon Tn 5 and allows the selection of genetically modified plants.	Bacterial transposon Tn 5	Berg <i>et al.</i> , 1975; Bevan <i>et al.</i> , 1983, 1984.
nos promoter	227	This fragment promotes the transcription of the <i>nptII</i> gene.	<i>A. tumefaciens</i> Ti plasmid	Hernalsteens <i>et al.</i> , 1980; Bevan <i>et al.</i> , 1983.

DNA Sequence				
Element	Size bp	Function	Origin	References
Right border	26	This border delineates the DNA transferred to plant cells	<i>A. tumefaciens</i> Ti plasmid	Zambryski <i>et al.</i> , 1980.
Various linkers	433			
Total nucleotides	4718			

#### Insert number

17. The Company provided Southern hybridisation evidence of DNA isolated from the primary transformants of the inbred line TGT7F that confirmed a single insert.

#### V. GENETIC STABILITY OF THE GMO USED AS A NOVEL FOOD SOURCE

18. The Company provided information to show that the primary transformant was selfed numerous times in order to produce the inbred line TGT7F. This line is genetically uniform and homozygous for the introduced genes. Once the inbred line was established, it was used to produce single cross hybrids (Nema 1401 F & H282 F). The hybrid seed was tested in field trials in 1992 and 1993 in Chile, USA (California), Portugal and Australia and in glasshouses in the UK. PG enzyme levels were analysed and the results show that the level of activity was consistently reduced in both the inbred line and hybrids compared to the unmodified controls as shown in Table II below:

**TABLE II – PG ENZYME LEVELS IN FIELD GROWN MODIFIED HYBRIDS DEVELOPED FROM TGT7F**

LINE	NEMA 1401 nmoles galacturonic	H282 acid/hr/mg protein
TGT7 unmodified control	46.1 +/- 6.2	61.0 +/- 8.8
TGT7F	3.4 +/- 0.5	3.8 +/- 0.8

19. The field trials in 1993 in Chile and 1993 and 1994 in California were used to evaluate the agronomic characteristics of the GM inbred and hybrids lines derived from it were evaluated. Observation sheets were used to record details of agronomic performance. No differences were observed between the GM hybrids and the unmodified plants in terms of field performance, disease susceptibility or plant morphology under different environmental conditions. The overall phenotypic assessment of the GM hybrids was indistinguishable from non-GM controls, except for the fruit quality, the difference being the increased viscosity that was the intended effect of the genetic modification. Pest and disease resistance characteristics were monitored throughout the trials. There were no differences observed between the GM and the non-GM control plants in susceptibility to the main tomato diseases in the field. However, it was observed that the ripe fruits of the GM tomato plants could withstand cracking to a greater degree than the non-GM

*Detailed descriptions of underlined words are contained in the Glossary*

tomato plants. This reduced the levels of opportunistic fungal infection that is prevalent on cracked fruit.

### Processing

20. The company has carried out processing experiments with the GM fruit under conditions ranging from laboratory through to pilot plant and full scale commercial production. The results presented show that the modification has caused the intended effect by producing a more viscous tomato paste at lower temperatures whilst retaining the integrity of peeled and diced products.
21. The results presented by the company of recent field trials in Italy (1996), Spain (1996 and 1997), France (1997) and Greece (1997), showed the consistent downregulation of PG enzyme activity, which demonstrates the stability of the introduced PG gene.

## VI. SPECIFICITY OF EXPRESSION OF THE NOVEL GENETIC MATERIAL

22. Both of the introduced genes are under the control of constitutive promoters and therefore are potentially expressed in all parts of the plant and during all growth stages. However, the PG enzyme is only produced at the onset of fruit ripening and is therefore only present in the ripe fruit.

## VII. TRANSFER OF GENETIC MATERIAL FROM GMO

23. The manufacture of the peeled and some comminuted products will result in a final product that contains seed. The company carried out germination studies on seed taken from GM peeled, processed products manufactured in Italy in 1995, alongside seed taken from unprocessed GM and non-GM tomato fruits. The results demonstrated that under standard germination conditions; the seed from the processed product was incapable of germination. Results shown in Table III.

**TABLE III – SEED GERMINATION OBSERVED IN PROCESSED PEELED TOMATOES**

Seed Sample		% Germination
11013	unmodified	0% (0/250 seeds)
11013F	modified	0% (0/250 seeds)
Alisa Craig		90% (225/250 seeds)

24. Although the raw tomatoes will contain the introduced DNA, these tomatoes are intended exclusively for processing, and the processed tomato products do not contain any functional DNA. The company produced data to demonstrate that after the thermal processing stage the *nptII* gene had degraded. Data also demonstrated that the *nptII* gene product could not be detected in tomato products after the manufacturing process. Therefore there is no risk of gene transfer to human gut flora through ingestion of the processed tomato products.

25. The *nptII* gene was isolated from the bacterial transposon Tn5 from the bacterium *E. coli* that are part of the natural human gut flora. The product of the gene is the APH(3')II enzyme that catalyses the transfer of a phosphate group from adenosine 5'-triphosphate (ATP) to hydroxyl group of the aminoglycoside antibiotics (neomycin, kanamycin etc.), thereby inactivating them.
26. The *nptII* gene is present in the fresh GM tomatoes as shown by polymerase chain reaction (PCR) analysis and Southern hybridisation. The *nptII* gene product APH(3')II and its co-factor ATP are also present in the fresh fruit as results of analysis conducted at Campden and Chorleywood Food Research Association (CCFRA) show. PCR analysis could not detect the presence of the gene in the processed tomato products, neither did enzyme linked immunosorbant assay (ELISA) analysis conducted at CCFRA detect the presence of the APH(3')II gene product. The levels of ATP were variable and probably reflected the physiological state of the fruit at harvest and the method of processing. The levels of ATP are unlikely to affect the fate of the APH(3')II protein after ingestion of the processed tomato products, as these were below the limits of detection. There is also no risk of gene transfer to the human gut micro-flora as the *nptII* gene was not detected in the processed tomato products. These results, along with data from Fuchs *et al* 1993<sup>5</sup>, support the conclusion that ingestion of processed plant products containing the gene and its APH(3')II protein product will not compromise the efficacy of orally taken aminoglycoside antibiotics.

#### IX. ANTICIPATED INTAKE/EXTENT OF USE OF THE NF

27. The company provided information on the intake and extent of use of tomatoes in the European Community based on the FAO Food Balance Sheets of 1984-86 and 1992-94<sup>6</sup> these include both fresh market salad tomatoes and processed tomato products. The company also quoted from The Tomato Market in OECD Countries (1992)<sup>7</sup> that indicates an average consumption of processed tomato products within the EU at 14 kg *per capita per annum*. As with conventional tomatoes, suitable climatic conditions for growth will restrict the growing region of the GM line geographically to the Southern European Member States, although, the final GM processed tomato products will be distributed through the EU. The company does not envisage any new uses or markets for the processed tomato products, as these products are expected to replace those from conventional tomatoes.

#### X. INFORMATION FROM PREVIOUS HUMAN EXPOSURE TO THE NOVEL FOOD OR ITS SOURCE

28. The tomato has been used in Europe for over two centuries, and has become widespread in its use both as fresh market cultivars and for processing into tomato products. Canned tomato paste produced from hybrids derived from TGT7F were placed on the market in the UK in 1996. These tomatoes were grown and processed on a commercial basis in California, USA. A total of 1.6 million cans have been sold up to the beginning of 1998, with no adverse health effects being reported by consumers. The cans were clearly labelled as a product of GM tomatoes (paragraph 6).

*Detailed descriptions of underlined words are contained in the Glossary*

**XI. NUTRITIONAL INFORMATION ON THE NOVEL FOOD**

29. The company has carried out comparative nutritional analysis on inbred and hybrid varieties of the GM line of both the fresh fruit and the processed products and in each case the appropriate non-GM controls and commercially available products were also compared. A comparison of the result with published ranges was also presented by the company. The results show that the genetic modification did not change the nutritional profile of the processed products.
30. The following nutritional components were analysed:
- moisture, ash, fat, total carbohydrate, available carbohydrate, total dietary fibre, soluble fibre, insoluble fibre, total sugars, protein, cellulose, hemicellulose, energy value;  
 Minerals: sodium, potassium, calcium, magnesium, phosphorus, iron;  
 Vitamins: A, E, B1, B2, niacin, B6, folic acid, C and;  
 malic acid, citric acid, lycopene.

**XII. MICROBIOLOGICAL INFORMATION ON THE NOVEL FOOD**

31. The GM procedure is not likely to result in any differences in the microbial content of the tomato products. In addition all processing is strictly controlled and no microbial contamination should occur. The products will be manufactured in accordance with all appropriate Codex specifications, EU food legislation and Good Manufacturing Guidelines.

**XIII. TOXICOLOGICAL INFORMATION ON THE NOVEL FOOD**

32. The tomato, *L. esculentum*, in common with other members of the family Solanaceae, is known to have the potential to accumulate naturally occurring toxins known as glycoalkaloids. The principal naturally occurring toxin in tomato is  $\alpha$ -tomatine, but the principal alkaloids of potato (solanine and chaconine) have also been found in tomatoes in low amounts. Tests conducted at CCFRA using non-GM fresh fruit, commercially available paste samples and non-GM paste as controls showed that the levels of the glycoalkaloid toxins in the GM fresh fruit were below the level of detection of 5mg/kg for solanine, chaconine and 15mg/kg for tomatine. The levels in the processed products were also below the level of detection of 5mg/kg except for the  $\alpha$ -tomatine in the paste. The paste produced from the GM inbred line had levels of 58 mg/kg, although this was still below that of the non-GM control, which had levels of 74 mg/kg.
33. Other naturally occurring toxins (tyramine, tryptamine, serotonin, histamine, nicotine and lectins) in the tomato were identified and the results of analyses conducted at the CCFRA showed that the levels in the paste obtained from the GM line were comparable with the commercial controls, and were often below the level of detection that varied between toxin from <0.1mg/kg for nicotine to 20mg/kg for histamine. This evidence demonstrated that the introduced genes had not had any effect on the levels of the naturally occurring toxin.
34. The company also had analyses conducted at CCFRA for the toxic metals: arsenic, cadmium, lead and mercury, as metal contamination of plants may arise naturally from the nature of the soil in which they grow or other agronomic practices. The results of the analyses showed that the level of toxic metal contamination of the GM fruit and products fell within the range of values obtained in the controls and commercially available tomato products.

*Detailed descriptions of underlined words are contained in the Glossary*



35. There were no reports found in a literature search carried out by the Company to show that the *nptII* gene and its associated APH(3')II protein are inherently toxic. The protein is also heat labile (Calgene Inc. 1990)<sup>4</sup> and degrades rapidly in the human gut (Fuchs *et al* 1993)<sup>5</sup>. Additionally, information presented by the Company showed that no detectable amounts of APH(3')II protein were present in the GM processed tomato products.

### Allergenicity

36. It is known that raw salad tomatoes can elicit allergenic responses in some people. However, the introduced gene products are not known allergens. In addition, the effect of the genetic modification is to reduce the levels of the PG enzyme produced in non-GM tomatoes and thus it would be expected that this would not have any allergenic consequences. The APH(3')II protein has not been detected in the processed products; also Fuchs *et al* (1993)<sup>5</sup> demonstrated that in simulated gastric fluids this protein is degraded rapidly. This implies that on ingestion, the APH(3')II protein would be degraded rapidly in the stomach of mammals, and therefore there is little potential for it to reach the intestinal mucosa and elicit an allergenic IgE response. No adverse health effects were reported from sales of the GM tomato paste to date (February 1998).

## General discussion

37. The Competent Assessment body for the UK Competent Authority, the ACNFP, has assessed the information presented by the company to support its application for processed products produced from TGT7F hybrids. The Committee considered information in accordance with the European Commission's guidelines to establish the safety of the GM tomato products for human consumption.
38. The Committee assessed information presented on the genetic modification procedures; it considered the stability of the insert, and the expression of the introduced genes. The Committee was satisfied with the data presented and agreed that only one insert had been introduced into the parental line, and that agronomic data from field trials conducted both inside and outside of the European Community had demonstrated the stability of the insert over several generations under differing environmental conditions.
39. Compositional (nutritional and toxicological) data satisfied the Committee that no differences existed between the GM tomato fruit or the processed tomato products produced from them and their non-GM counterparts. This was further evidence that no secondary effects had occurred as a result of the genetic modification.
40. The Committee considered the introduction of the *nptII* gene into the GM tomato. Analyses show that although the *nptII* and its gene product are present in the GM fresh fruit, the thermal processing that the fruit undergoes to produce the final products, degrades both the gene and its protein product to a non-functional state. The safeties of the antibiotic resistance gene, *nptII* and its protein product have been well documented in published research papers.
41. A processed product (tomato paste) derived from the GM tomato hybrids grown in California, has been on sale in the UK since February 1996 and no adverse health effects have been reported by the consumers of the product. This product and all the intended processed products produced from the GM tomatoes will be clearly labelled as being produced from a GM source.

## Conclusion

42. A thorough assessment of the GM tomatoes, and the processed products derived from them, has revealed no safety concerns arising from the modification and the Committee therefore concludes that the processed products are as safe for human consumption as processed products obtained from non-GM tomatoes.

## References

1. Commission of the European Communities 1997: Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation (EC) No. 258/97 of the European Parliament and of the Council. C(97) 2634 final.  
*Official Journal of the European Communities* Vol. 40 L253/1-45 16 September 1997.
2. ZENECA Plant Science 1998: [Appendix II] Application to the United Kingdom Advisory Committee on Novel Foods and Processes for evaluation of the safety of processed products derived from genetically modified tomatoes. Dossier provided by Camilla Beech, European Biotechnology Regulatory Manager, ZENECA Plant Science, Jealott's Hill Research Station, Bracknell, Berkshire, RG42 6ET (Nigel Poole will be responsible for the dossier from March-July 1998).
3. Bevan M W (1984): Agrobacterium vector for plant transformation. *Nucleic Acids Research* 12: 8711-8721.
4. Calgene Inc. (1990): Request for advisory opinion *Kan<sup>r</sup>* gene: Safety and use in the production of genetically engineered plants. FDA Docket Number 90A-0416.
5. Fuchs R L *et al* (1993): Safety assessment of the neomycin phosphotransferase II (NPTII) protein. *Bio/Technology* 11: 1543-1547.
6. FAO Food Balance Sheets (1996), Rome.
7. OECD (1992): The Tomato Market in OECD Countries. OECD Publications, Paris, 80-81.

# Appendix III

## Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to GM chicory

Your reference:

Our reference: NFB 88

23 December 1998

Mr A Klepsch  
European Commission  
DG III  
Rue de la Loi 200  
B-1049 Brussels  
Belgium  
Dear Mr Klepsch

### Placing on the market of transgenic radicchio rosso and green hearted chicory

The Competent Food Assessment Body for the UK Competent Authority, the Advisory Committee on Novel Foods and Processes (ACNFP), has considered the initial report from the Dutch Competent Authority for the placing on the market of transgenic Radicchio rosso and green hearted chicory. The UK Competent Authority wishes to raise the following objections to the marketing of this product:

- i) the Dutch Competent Authority's report does not address the labelling of these products and foods containing them; and
- ii) there is some ambiguity in the application. The UK Competent Authority wishes to make it clear that approval for environmental cultivation cannot be obtained under the Novel Foods Regulation 258/97. Before the chicory can be grown in the EU for food use, approval for environmental cultivation should be pursued under the EC Directive on the deliberate release into the environment of genetically modified organisms 90/220/EEC;
- iii) the Company's summary document and the Dutch Competent Authority's opinion provided insufficient information for the ACNFP to reach a conclusion on the safety of the products so additional information was requested from the Company. The ACNFP considers that this additional information does not adequately address its concerns about harmful, unintended secondary effects from the genetic modification on phenotype and composition. These issues need to be resolved before the UK Competent Authority can agree to the marketing of these products.

The ACNFP's specific concerns are:

- a) A marker gene encoding resistance to streptomycin and spectinomycin was included during formation of the construct. The molecular data supplied does not conclusively demonstrate that only the desired DNA was transferred into the GM

plants and that this marker is absent. The Committee considers that the PCR analysis used by the company is inappropriate in this case and that Southern blot analysis using the entire marker gene as a probe should be carried out.

- b) Further data on composition and phenotype is needed. It is the company's responsibility to establish that the range of compositional variation in a population derived from GM technology is equivalent to that for non-GM populations. These species produce bitter compounds which may have a biological effect. There are reports of possible harmful consequences following contact with or consumption of chicory and there is a suggestion that sesquiterpene lactone is the cause. There are well-established methods with which to measure sesquiterpene lactones and such data would reveal unintended effects on a relevant facet of secondary metabolism. Data on amino-acids and biogenic amines would also provide reassurance that metabolic disturbance had not taken place as an unintended consequence of DNA integration and foreign gene expression.

I look forward to your early response to our objections.

Yours sincerely

Mr N Tomlinson  
Additives and Novel Foods, Branch 'C'  
**MAFF**

# Appendix IV

## Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to products from *Stevia Rebaudiana* Bertoni

Dr F Campoli  
DGIII/E/i  
Rue de la Loi  
B-1049 Brussels  
Belgium

19 October 1998

Dear Mr Campoli

### **Evaluation of *Stevia rebaudiana* Bertoni as a novel food**

The UK Competent Authority has examined the opinion from the Belgian CA on this application and agrees with the conclusion they reached, that the data provided are inadequate to support approval of this material as a novel food. We share their concerns regarding this application and note particularly the lack of information on:-

- i) the estimates of likely intake of the material;
- ii) the specification for the material, which is inadequate, particularly in terms of the level of stevioside. We would normally expect to see the results of analyses of at least three batches of material to demonstrate that the material to be sold is of a consistent composition;
- iii) the extent to which the active component stevioside is metabolised by human gut bacteria and the possible toxicological consequences of such metabolism.

We also note that the active component stevioside has been evaluated previously by both the EC Scientific Committee for Food and also by the Joint FAO/WHO Expert Committee on Food Additives (earlier this year) and that both have concluded that the toxicological data available were inadequate.

After our expert advisory committee had examined the opinion of the Belgian CA, we received the additional information contained in a revised application from Prof Dr J M C Geuns, that was circulated with the papers for the Standing Committee meeting on 28/29 October. We assume that submission of these additional data will now result in all the information being referred to the Scientific Committee for Food, as laid down in the provisions of the Novel Food Regulation. However we would make the following points about the additional information provided:

- i) the specification and analytical data are still not adequate to provide reassurance that this is a consistent product;
- ii) many of the studies quoted on page 12 of the revised document are conducted on "*Stevia* extract" but the composition of this extract is not described;

- iii) the subacute and chronic toxicity studies are conducted on stevioside rather than the dried plant material and there is still a lack of evidence on the extent to which stevioside present in the dried plant material might be metabolised by human gut flora and the toxicological consequences of this in terms of the formation of steviol.

We welcome the opportunity to discuss this application at the Standing Committee for Foodstuffs meeting on 29 October.

Yours sincerely

Mrs S J Hattersley  
UK Competent Authority (EU Regulation 258/97)

# Appendix V

## Letter to European Commission containing UK Competent Authority comments on the data presented in the application relating to phospholipids from egg yolk

Your reference:

Our reference: NFB 253

23 December 1998

Mr A Klepsch  
European Commission  
DG III  
Rue de la Loi 200  
B-1049 Brussels  
Belgium

Dear Mr Klepsch

### **phospholipids from egg yolk**

The Competent Food Assessment Body for the UK Competent Authority, the Advisory Committee on Novel Foods and Processes (ACNFP), has considered the initial report from the Belgium Competent Authority for the placing on the market of Phospholipids from egg yolk. The UK Competent Authority wishes to raise the following objections to the marketing of this product:

- i) neither the Belgium Competent Authority's report nor the Company's dossier address the labelling of these products and foods containing them;
- ii) from the papers provided, the specification of the product is not complete and no mention is made regarding the presence of dry protein in the final product; and
- iii) there is insufficient nutritional and toxicological information in the dossier, especially regarding the structural similarity of the phospholipids with those in existing diets. No evidence has been provided on bioavailability or the absence of adverse effects.

Yours sincerely

Mr N Tomlinson  
Additives and Novel Foods, Branch 'C'  
MAFF

# Appendix VI

## Letter to European Commission containing UK Competent Authority decision on camelina oil

Your reference:

Our reference: NFB 18

25 September 1998

Dr A Klepsch  
European Commission  
DG III  
Rue de la Loi 200  
B1049 Brussels  
Belgium

Dear Dr Klepsch

### **Camelina oil – consideration of status**

I am writing to inform you of the opinion of the UK novel foods competent authority regarding the status of Camelina oil with respect to the Novel Foods and Novel Food Ingredients Regulation EC No 258/97.

In June this year an enquiry was received from the company John K King & Sons Ltd. regarding the use in food of several oils, including oil from the plant *Camelina sativa*. This crop is a member of the Cruciferae family which is being developed as an oilseed crop for northwest Europe with food and technical applications.

Camelina oil received approval in France for use in food in May this year and copies of two relevant documents are attached; a translation of the letter from the French Ministry of Economic Affairs, Finance and Industry and the comments of ITERG (the Technical Institute for Research into Fats and Oils) on the possible use of camelina oil for human feeding. The letter indicates that the French authority does not class Camelina oil as novel and considers that it meets edible quality standards.

From the initial information, it seemed likely that this oil would fall within the scope of Article 1(2) (e) of the Novel Foods Regulation. Having received this advice, the company requested a meeting in order to discuss this oil and a potential application for approval for its use in food. At this meeting we were informed that Camelina was produced in Europe in the early twentieth century, up until the 1950s, for both edible and technical applications. However, its use declined due to the development of rapeseed and its low productivity in comparison to this plant. An article from *Lipid Technology* is attached for information, as is an information sheet from the company.

This oil clearly has a history of food use within the EU, albeit prior to any system for the safety evaluation of novel foods and with no evidence of consumption in Europe since the 1950s. Therefore, it is considered that a decision not to class this as a novel food can be justified. The UK Advisory Committee on Novel Foods and Processes have considered the data on this oil and are content that it should not fall under the scope of the Novel Foods Regulation.



However, the Committee noted that, as for all foods, Camelina oil will be subject to the provisions of the Food Safety Act 1990.

Yours sincerely

Miss Tracy Boshier  
Additives and Novel Foods Division, Branch 'C'  
**MAFF**

# Appendix VII

## Letter to European Commission containing UK Competent Authority decision on FRUITRIM®

Your reference:

Our reference: NFB 18

25 September 1998

Ms Joyce Bell  
HAX Limited  
306 Archway Road  
London N6 5AU

Dear Ms Bell

### **FRUITRIM® – fat replacer**

As previously agreed, I am writing to advise you of the opinion of the UK novel foods competent authority with regard to the status of FRUITRIM®. I apologise for the delay in this response.

From the information you originally provided it was not clear whether FRUITRIM® would fall under the scope of the Novel Foods Regulation. This is because the intended use of the product as an ingredient to replace solid and liquid fats is novel in that a fruit juice/starch product is to be used to replace fat. In addition, the process used to manufacture this product (which involves the reduction of the water contents of the components) is patented and thus different in some way from conventional technologies.

Also, launching a product in April 1997 (i.e. a month prior to the implementation of the Novel Foods Regulation) would not be likely to constitute a history of use in the EU before 15 May 1997 (although it would be for the Commission to give the definitive opinion on this).

However, in several fax messages, you provided some additional information and emphasised that after extensive discussions with the manufacturer, you do not consider that FRUITRIM® falls within the scope of the Novel Foods Regulation for a number of reasons:

- (a) FRUITRIM® is a simple mixture of two components, both of which are regarded as food ingredients in Europe and can be readily obtained from commercial sources. They are consumed throughout Europe and pose no danger to consumer health;
- (b) Although the manufacturing process and ingredients of FRUITRIM® are unique enough to warrant protection under US patent law, such protection does not make the product 'novel' for food regulation purposes; and
- (c) The manufacturing process involves the reduction of the water contents of the ingredients to a minimum of 77% soluble solids, which is not itself a novel technology, and there is no reason to believe that this process would alter the chemical or nutritional properties of the ingredients.

Having carefully considered all the information provided I can confirm that, in the opinion of the UK competent authority, FRUITRIM® would not be regarded as a novel food.

As discussed, this letter will be copied to the Commission in order that other Member States can be informed.

Finally, I would like to remind you that all foods are subject to the requirements of the Food Safety Act 1990.

Yours sincerely

Miss Tracy Boshier  
Additives and Novel Foods Division, Branch 'C'  
**MAFF**

# Appendix VIII

## Statistically valid data to support safety clearance of crop products under the Novel Foods Regulation (258/97)

PAPER FOR CONSIDERATION BY THE EUROPEAN COMMISSION: STATISTICALLY VALID DATA TO SUPPORT APPLICATIONS FOR SAFETY CLEARANCE OF CROP PRODUCTS UNDER EC REGULATION ON NOVEL FOODS AND NOVEL FOOD INGREDIENTS 258/97

### Purpose

1. This paper is intended to promote discussion about the provision of statistically valid data in applications for product approvals under the EC Regulation on Novel Foods and Novel Food Ingredients 258/97 (EC Novel Foods Regulation). This issue has been considered by the UK Competent Authority's competent food assessment body, the Advisory Committee on Novel Foods and Processes (ACNFP), and the paper presents the ACNFP's conclusions.

### Introduction

2. The European Commission's guidelines<sup>(1)</sup> which accompany the EC Novel Foods Regulation have been welcomed by potential applicants for product approvals under the Regulation. The European Commission's guidelines give a clear indication of the type of data that is needed to form the basis of a safety assessment and the UK Competent Authority has incorporated the relevant sections from the guidelines into its computerised decision tree.
3. However, the European Commission's guidelines do not include advice on the appropriate sample sizes to be included in data submitted in an application for approval under the Regulation. The ACNFP is concerned that all safety assessments should be based on statistically valid data and has outlined its conclusions in this paper.

### Background

4. The report of a recent FAO/WHO expert consultation on biotechnology and food safety<sup>(2)</sup> states that for food safety assessment purposes:  
  
"Substantial equivalence is established by a demonstration that the characteristics assessed for the genetically modified organism (GMO), or the specific food product therefrom, are equivalent to the same characteristics of the conventional comparator. The levels and variation of characteristics (e.g. phenotypic and composition characteristics etc.) in the GMO must be within the natural range of variation for those characteristics considered in the comparator and be based upon an appropriate analysis of data."

### Natural variation

5. The natural variation of a range of measured attributes or comparators may be large because of the wide variation in conditions, such as soil fertility, temperature, light or water availability, under which crops are grown. The issue may be compounded by other effects including agronomic treatments to the growing crop, such as herbicide applications to a

herbicide tolerant crop, or post-harvest stress during storage (e.g. for potatoes stored in clamps).

6. Natural variation may obscure the differences between possible comparators for crops grown under identical conditions. The differences between the comparators of a GM crop and those of its non-GM control grown under identical conditions should be used to construct the criteria which determine whether a GM crop may be considered to be substantially equivalent to its non-GM control. Thus, for example, the mean of a comparator should be within a certain percentage of the control mean. The range of values quoted in the literature to express natural variation should be considered to be of secondary importance.

### **Specification**

7. The companies which request the safety assessment of GM foods or ingredients are, usually, technology providers and not the processors of the final or intermediate food products or ingredients; they often have no control over the specification of the final food ingredient. Consequently, proximate and detailed chemical analyses of the unprocessed sources of GM foods or ingredients are an important part of the safety assessment. Proximate and detailed chemical analyses required are analyses of fat, fatty acid profile, solvent extracted non-saponifiable matter, protein, amino acid profile, micronutrients, antinutrients, crude fibre, ash, and moisture contents.
8. Significant differences between the results of proximate and detailed chemical analyses of a GM crop product and its non-GM control may be an indication of secondary or pleiotropic effects and such changes would need to be investigated further.

### **Confidence limits and sample sizes**

9. The following methodology assumes that the differences in means between the GM crop and its control are independent for each measured comparator. A GM crop is considered to be substantially equivalent to its non-GM control when the difference between the underlying means fulfils some criterion for each measured comparator. Even if a GM crop is not substantially equivalent to its control, it is still possible that the differences between the observed means from a field trial could fulfil all the criteria for equivalence. The likelihood that this may happen can be estimated. If this probability is very small, we can say that there is evidence that the GM crop is substantially equivalent.
10. The test for substantial equivalence can be performed by constructing confidence intervals for each measured comparator. The test finds the GM crop to be substantially equivalent if each confidence interval is completely within the criterion for that comparator. By convention, 95% confidence intervals are commonly used. However, 99% and 99.9% confidence intervals are also used when greater certainty that the true value of the estimate is within the interval is required. The width of the interval is greater for higher levels of confidence.
11. Clearly, there are two important criteria which need to be set, namely the appropriate confidence interval to use in the test and the sample size. It is recommended that the Commission seeks EU-wide agreement on the most appropriate confidence interval. It may be considered necessary to alter the confidence interval used in the assessment according to the comparator under consideration and the potential hazard that it presents. It is in the applicant's interest to ensure that an adequate number of samples are analysed to reduce the chances that substantially equivalent GM products are deemed to be not substantially equivalent to their non-GM controls.

### **Trial sites, years and replicates**

12. For crop varieties which are intended to be grown commercially in the EU, the location of trial sites should be representative of the range of environmental conditions under which the varieties would be expected to be grown. The number of trial sites should be sufficient to allow accurate assessment of agronomic and compositional characteristics over this range. Similarly, trials should be over a minimum number of years to allow adequate exposure to conditions met in nature. It is recommended that the minimum number of years and the minimum number of trial sites should be set by the EU competent authorities and agreed by the Commission. The UK recommends that the minimum number of sites should be six and the minimum number of years should be two.
13. Replication at each trial site is necessary to ensure that environmental effects at a single location are minimised and to allow the adequacy of statistical models to be checked. To reduce any effect from naturally occurring genotypic variation within a crop variety, the minimum number of replicates used should be not less than three and will need to be appropriate to the crop species under trial. Trials carried out by the National Institute of Botany in the UK, which assesses crop varieties for the UK National List of recommended plant varieties, require three replicates at each trial site for GM maize and four replicates at each trial site for GM spring oilseed rape. To allow effective comparison, the GM crop and its non-GM counterpart should be grown in adjacent plots at the same site and at the same time.
14. Data from the different sites should not be pooled before being statistically evaluated. Data from each site should be evaluated separately to allow information on each individual site to be provided as part of the dossier.

### **Conclusions**

15. Statistically valid data is necessary for the effective comparison of a GM crop with a non-GM control. The use of such data will minimise the effect of natural variation and will indicate whether there are any differences between the GM crop and the non-GM control which require further investigation.
16. The ACNFP recommends that GM crops are trialled under the range of environmental conditions in which it is intended that the crop should be grown commercially. A minimum of six sites should be used, with the number of replicates to be determined for individual crop species. A larger trial, which would provide more information, may be necessary in some cases. Trials should be carried out for a minimum of two successive years.

### **References**

1. Commission Recommendation of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under regulation (EC) No 258/97 of the European Parliament and of the Council.
2. FAO/WHO (1996) Biotechnology and food safety: Report of a Joint FAO/WHO Consultation, Rome, Italy, 30 September – 4 October 1996. FAO Food and nutrition Paper 61.

# Appendix IX

## The role of toxicological studies in assessing the safety of novel foods for humans

### Summary

1. There has been much media interest in the safety of GM foods in recent months with several groups, including consumer and environmental Non Governmental Organisations suggesting that all GM foods should be subject to long term animal feeding studies before approval.
2. This paper was considered by the ACNFP at its 39th meeting on 24 September 1998. It briefly reviews the role of toxicological studies in the safety assessment of GM foods and focuses on the pros and cons of subjecting such foods to long term feeding studies. It does not aim to address the testing of novel foods for possible allergic reactions which is a separate, specialised, safety issue.
3. The Committee considered 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 as complicating factors, in the design and interpretation of such 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. Nevertheless, a detailed data package must be provided under EU Guidelines to facilitate a rigorous safety assessment and the appropriateness of long term feeding studies is considered on a case by case basis.

### Background

4. Animal studies are a major element in the safety assessment of many compounds such as pesticides, pharmaceuticals, industrial chemicals and food additives. In most cases, the test substance is well characterised, of known purity, of no nutritional value and human exposure is generally low. It is therefore relatively straightforward to feed such compounds to animals at a range of doses, some several 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.
5. By contrast, foods are complex mixtures of compounds characterised by wide variation in composition and nutritional value. Due to their bulk and effect on satiety they can usually only be fed to animals at low multiples of the amounts that might be present in the human diet. In addition, a key factor to consider in conducting animal studies on foods is the nutritional value and balance of the diets used, to try to avoid the induction of adverse effects which are not related 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. Another consideration in deciding the need for animal studies is whether it is appropriate to subject experimental animals to such a study if it is unlikely to give rise to meaningful information.

6. 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 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.

### Safety assessment of novel foods

7. One of the first novel foods to be formally assessed in the UK was the mycoprotein 'Quorn'. At roughly, the same time the safety of irradiated foods was assessed through a vast array of animal feeding studies. In both cases practical difficulties were encountered. In contrast to many non nutritive substances, foods are intended to be consumed by man at levels which approach the maximum dose that could be used in animal studies. Toxicological studies are designed to characterise the toxicological profile of individual chemical substances not complex substances such as foods. Long-term feeding of high levels of individual 'foods' to animals can result in nutritional imbalances which make interpretation of such studies extremely difficult. Table 1 compares the differences between the safety assessment of chemicals and foods.

**TABLE 1: DIFFERENCES BETWEEN CHEMICAL AND FOOD TOXICITY EVALUATION<sup>1</sup>.**

Chemical	Food
Material usually simple, chemically precise substance	Complex mixture of many compounds
Highest dose level should produce an effect	Effects improbable at the maximum dose level that can be incorporated in the diet for the test species
Small dose (usually less than 1% of diet)	High intake (usually greater than 10%)
Easy to give excessive dose	Intakes above those normally present in the diet difficult
Acute effects obvious	Acute effects difficult to produce (usually absent)
Generally independent of nutrition	Nutrition dependent
Specific route of metabolism simple to follow	Complex metabolism
Cause/effect relatively clear	Cause/effect, if observed at all, may be confused

### Substantial Equivalence

8. Recognising that traditional safety assessment techniques based on toxicological testing may not be applicable in the case of most foods or food ingredients produced by biotechnology the FAO and WHO held a consultation in 1990 to address the problem.
9. This recommended that safety assessment strategies be based on a consideration of the molecular, biological and chemical characteristics of the food to be assessed and that this should determine the need for, and scope of, traditional toxicological testing.
10. The consultation also established the comparative principle whereby the food being assessed is compared with one that has an accepted level of safety. In 1991 the OECD<sup>3</sup> expanded upon this and formulated the concept of substantial equivalence. This was based on the concept that if a food or food ingredient under consideration can be shown to be essentially equivalent in composition to an existing food or food ingredient then it can be



assumed that the new food is as safe as the conventional equivalent. The WHO and FAO refined the concept at an expert consultation meeting held in Rome in 1996. In the report of this meeting<sup>4</sup> 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.'

11. 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'. This approach to the assessment of GM foods is now accepted and applied worldwide.
12. Following a comparison of the GM product with a conventional counterpart, three outcomes are possible:

The GMO or food product obtained from it is substantially equivalent to a conventional counterpart.

The GMO or food product obtained from it is substantially equivalent to a conventional counterpart except for a few clearly defined differences.

The GMO or food product obtained from it is not substantially equivalent to a conventional counterpart – either because the differences cannot be defined or because there is no existing counterpart to compare it with.
13. Where a food can be shown to be substantially equivalent it is considered to be as safe as its counterpart and no further safety assessment is required. Where there are clearly defined differences between the GM food and its conventional counterpart the safety implications of the differences need to be fully assessed. Where a food is not substantially equivalent it does not mean that the food is unsafe. However, there would be a need for extensive data (which might include the results of animal feeding studies if considered appropriate) to be provided before the product's safety can be fully assessed.

#### **ACNFP Decision tree**

14. In 1990 the ACNFP developed a decision tree to indicate the types of information that were likely to be required for individual novel foods. This leads into a series of structured questionnaires depending upon the exit point. The ACNFP considered the role of animal studies in the safety assessment of novel foods when constructing this approach. At that time, it was decided that, while such studies could be an important tool in the testing armoury in certain specific circumstances, they were not likely to be universally applicable

for the reasons given earlier. The Committee reaffirmed this view when it reviewed the decision tree in 1994 following a public consultation exercise.

15. To ensure that all member states follow a similar approach to the safety assessment of novel foods, the SCF has recently produced a detailed set of guidelines setting out the type of information that would be expected to support an application for approval of a novel food. These guidelines draw upon the structured approach developed by the UK's ACNFP. The need for animal studies is considered on a case by case basis.

## Conclusions

16. The ACNFP's approach to the safety assessment of novel foods, based on the concept of substantial equivalence, is fully consistent with the guidelines that accompany the EC Novel Foods Regulation and mirrors those used elsewhere in the world.
17. Animal tests represent an important tool in certain specific circumstances but the need for them should continue to be decided on a case by case basis. There is no scientific justification for insisting that all GM foods should be subject to long term feeding studies as such an approach would be unlikely to produce meaningful information in the vast majority of cases.

## References

1. Based on a paper in OECD 1996 Food Safety Evaluation, *OECD*, Paris
2. Strategies for assessing the Safety of Foods Produced by Biotechnology. Report of a joint FAO/WHO consultation, *WHO Geneva* 1991
3. Safety Evaluation of Foods Produced by Modern Biotechnology – concepts and principles, *OECD* Paris 1993
4. Biotechnology and Food Safety, Report of a joint FAO/WHO consultation Rome 30 September – 4 October 1996, *FAO Food and Nutrition Paper* 61 1996

# Appendix X

## Note of the meeting of the joint ACNFP/COMA ad hoc working group meeting on the dietary implications of cumulative nutritional changes in individual novel and conventional foods

### JOINT MEETING OF COMA AND ACNFP

#### DIETARY IMPLICATIONS OF CUMULATIVE NUTRITIONAL CHANGES IN INDIVIDUAL NOVEL AND CONVENTIONAL FOODS

THURSDAY 10 SEPTEMBER at 12.30pm in THE OLD LIBRARY ROOM,  
RICHMOND HOUSE

**Chair:** Dr P Troop

**COMA Members:** Professor P Aggett \*  
Professor A Jackson  
Professor D Richardson  
Dr A Williams

\* also a member of ACNFP

**ACNFP Members:** Professor J Bainbridge  
Professor T Sanders  
Mrs E Russell

**Other members:** Mr N Poole BSPB – Zeneca Plant Sciences  
Ms G Fine British Retail Consortium – Sainsburys  
Dr A Robertson British Retail Consortium – Safeway  
Mr D Favell Food and Drink Federation – Unilever Research  
Mr P Strachan Food Advisory Committee  
Mr P Wagstaffe European Commission Scientific Committee for Food

**Observers:** Mr B Knock (MAFF)  
Dr J Bell (MAFF)  
Mr N Tomlinson (MAFF)  
Professor M Wiseman (DH)  
Dr S Reddy (DH)

**Secretariat:** Mrs S Hattersley (ACNFP)  
Dr A Redfern (COMA)

#### Welcome and Apologies for absence

1. Apologies were received from Dr P Dale (ACNFP) and Professor P James (COMA). The Chairman welcomed those present to the meeting. She invited members to introduce themselves. It was agreed that the minutes of the meeting would be made public, and would be submitted to the ACNFP and COMA for consideration.

## Introduction

2. The issue of the cumulative effect of a number of gradual, possibly individually trivial, changes in the composition of foods and food ingredients was highlighted recently when the ACNFP was asked to consider a new variety of linseed *Linium usitatissimum*, that had been developed to produce an oil with a reduced level of  $\alpha$ -linolenic acid. This oil had been developed by traditional plant breeding. As oil from this variety of linseed had been on sale in other Member States for a number of years, it was concluded that it was not a novel food, as defined by the EC Novel Food Regulation. Concern was expressed that the composition of some foods and food ingredients was gradually and legitimately being altered to meet technical and commercial needs but that the wider nutritional implications of the cumulative changes might not be receiving due attention, and that in the case of conventional foods no formal mechanism existed for such scrutiny. Additionally cumulative effects of interactions between nutrients should be considered.
3. The group was asked:
  - to consider the inequity in assessment of novel and non-novel foods;
  - whether there was concern over recent, and likely future changes;
  - what controls, if any, are necessary.

## Consideration of the current position

4. The group discussed the fact that changes in food composition can result from different animal breeding and farming practices or changes in the composition of animal feedingsuffs e.g. changes in the fatty acid content of farmed and wild salmon. There was concern expressed that consumers would be unaware of these subtle changes, though they might have significant health implications (either beneficial or adverse).
5. The assessment of novel foods is undertaken on a case-by-case basis and it may also be helpful to look at the overall picture. The extent and nature of the food supply is rapidly changing and so influencing food choice, and consequently nutrient consumption e.g. changes in the processing of commonly available foods such as increased use of sunflower oil and decreased use of hydrogenation.
6. There was a general view that the rate of change was accelerating, particularly in the area of functional foods, where the addition of physiologically active components could potentially have significant effects. The group was informed that the EU was in the early stages of developing Codes of Practice for labelling of and health claims for functional foods.
7. The group thought it was necessary to have an idea of consumption levels as a point of reference and a means of categorising high consumers. The group thought it was necessary to consider the upper limit of safety of consumption of such foods. The key drive in changes in food composition has been Government advice for a reduced fat content of the diet. However, this could lead to consequent changes in the sugar or fibre content of the product, which would still be sold on it's virtues as a low fat product with no reference being made to the other changes. It was noted that when products are fortified the level of fortification not only varies between brands but also depending on the type of food being fortified. For example folic acid fortification can be monitored in bread and breakfast cereals but as the extent of fortification increases to other foods there is a need to monitor the cumulative effects of such practices.

8. The consensus of the group was that changes have occurred, are continuing to occur and the rate of change is likely to accelerate. Some of these changes will be helpful with respect to public health, some neutral and some potentially harmful.
9. The group considered information to be important so that consumers could make a choice.

#### **Monitoring changes**

10. The group agreed that methods of monitoring changes would vary according to whether ingredients, products or the diet as a whole were being assessed. There was some support for a targeted approach focusing on priority areas.
11. The group were informed that the EU Novel Food Regulation had now been in place for over a year but, because up to now approval for use of novel foods has involved use of the notification procedure (which does not require the involvement of the SCF), there is no single body which can make a broad assessment of cumulative dietary changes due to Novel Foods at EU level. It was agreed that the nutritional impact of the changes from novel foods were currently small in comparison to those from conventional foods.
12. The group acknowledged that systematic nutritional surveillance of changes in food composition was currently limited and much of the information is supplied by ingredient/food manufacturers. In order to monitor future changes effectively there has to be some means of anticipating where the most significant changes are likely to occur. Some of the impetus for change comes from Government committees and reports. For example the Health Education Authority's (HEA) logo for good sources of folic acid has led to an increase in the number of products fortified with this vitamin. Monitoring such initiatives might enable areas where change is likely to occur to be more easily identified.
13. The group recognised that food composition tables are not a true reflection of the current composition of foods – there is a lag period between the changes and the updating of the databases/tables.
14. For changes resulting from plant breeding access to the National List or Common Catalogue would provide data on all new varieties on the European market that have been approved. However, nutritional changes would only be indicated on the list if this was the primary reason for the development of the new crop variety not if it was a consequence of another change, such as disease resistance or climatic tolerance.
15. It was suggested that the group should focus on those foods most people eat. Manufacturers tend to use the same ingredients so any change in their composition could potentially result in major changes in the nutrient content of the national diet. For example the selenium content of bread has declined substantially over time due to the increasing use of European rather than North American wheat. Change can be monitored by looking at typical diets but in addition the diets of extreme consumers and ethnic minorities need to be considered. However, Total Diet Studies are not necessarily sensitive indicators of change because of their ad-hoc nature. Additionally, whilst unexpected changes might be picked up by such studies to be certain of being able to do this a more comprehensive approach is required.
16. The group agreed that successful monitoring depended mainly on changes being notified. There is also variability in the magnitude of change and the question is what size of change over what timescale might be of concern. The group recognised the need to be aware of social trends that could have an impact on dietary choices i.e increased consumption of convenience foods. Additionally the number of major retailers distributing food is small

and this will result in some standardisation. The group was informed that detailed purchasing data were collected by the major supermarket chains but were not collated centrally.

17. The group agreed that a co-ordinated approach to gathering information on changes is required. Different systems are required for ingredients, products and whole diets. The group discussed ways of achieving this, including:
  - reporting/ notification by ingredient suppliers;
  - reporting/ notification by food manufacturers;
  - monitoring of whole diets by Government e.g. average and extreme consumers.
18. From the industry /retailer point of view this approach assumes good nutritional data is kept on all products. However, this is a dynamic area with products going in and out of the market. Additionally, it is dependent on the nutrient databases being up to date. There would have to be a good reason for keeping the data. Other useful databases that could be utilised are the food intolerance database and the HEA folic acid database.
19. The group concluded that even substantial changes in one food could lead to only small changes in relation to the total diet. On the other hand some changes in staple foods could be important, as could cumulative trends.
20. The importance of considering vulnerable groups was also highlighted. The group considered that a non-statutory system of alerting Government to these changes would be preferred, but a single contact point in Government is required for this to work effectively.
21. The group concluded that:
  - changes are occurring, but as the diet is robust individual changes may have a minimal impact on the whole diet, may take some time to become significant and may either have an additive effect or balance each other out;
  - change is happening at an accelerated rate and there may be interactions between nutrients;
  - the changes (e.g. novel foods, functional foods, new breeding approaches) need to be kept under surveillance and their further evaluation should be proportionate to the associated risks;
  - a large amount of data, particularly but not only in the food industry, is already available.

### Way forward

22. The group suggested a framework of proposals as a possible way forward including the need to:
  - build on the currently available systems of data collection both in Government and industry e.g. National Food Survey, Diet and Nutrition Surveys, Total Diet Study, updating food composition tables. Greater routine dialogue should be established between industry and DH/MAFF/FSA;
  - there should be an agreed focal point to which any change considered significant could be notified by industry, government, academia or consumer groups;
  - review the potential role of the Total Diet Studies as a tool to monitor changes in the total diet that might come from cumulative changes and whether they could also be used to monitor the diets of particular vulnerable subgroups;
  - prioritise areas of specific concern that should be monitored.

# Appendix XI

## Letter from ACNFP to US Food and Drugs Administration (FDA) on 'Guidance for industry: use of antibiotic resistance marker genes in transgenic plants'.

Your reference:

Our reference: ACNFP/39/11

4 December 1998

Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Rm. 1061  
Rockville  
MD 20852

Dear Sir

### **GUIDANCE FOR INDUSTRY: USE OF ANTIBIOTIC RESISTANCE MARKER GENES IN TRANSGENIC PLANTS**

Thank you for the opportunity to comment on the above document. The UK's Advisory Committee on Novel Foods and Processes (ACNFP) has discussed the paper. Committee members felt that the paper was well presented and would be of interest to the educated lay reader, as well as to the scientific community. Several Committee members had specific comments on the text, which are recorded below, including suggestions which might give the document a broader scope and make it comprehensive.

#### **Summary of the Consultation**

##### **A. *Direct Effects of Ingestion of Enzymes Encoded by Antibiotic Resistance Marker Genes***

The third paragraph states:

"With respect to whether an antibiotic resistance gene product found in food could compromise therapy with a clinically useful antibiotic by inactivating it in situ, some assurance against this possibility could be obtained by showing that the gene product is readily digestible or is inactivated by processing methods used by food producers."

The next paragraph follows on to say:

"In the case of animal feed it is likely that production methods will denature the enzyme thereby rendering it inactive against the antibiotic."

It should be remembered that while the production methods both for food and animal feed may denature the gene product, people may be exposed to it before this stage. For example when a plant is grown or when people are actually engaged in the production process.

**B. *Potential Transfer of Antibiotic Resistance Marker Genes to Gut Micro-organisms***

Paragraph one states:

“Transfer is considered to be unlikely because the DNA is degraded by nucleases and even if some were to survive digestion and were transferred integrated and expressed, epithelial cells are short lived and would slough off to be replaced by untransformed cells.”

The ACNFP considers this to mean the risk of transfer is small but finite. Functional gene transfer from bacteria to mammalian cells is certainly possible. Two relevant papers are:

1. Grillot-Courvalin C., Goussard S., Huetz F., Ojcius D. M., Courvalin P., 1998. Functional gene transfer from intracellular bacteria to mammalian cells. *Nature Biotechnology* 16: 1-5.
2. Naked DNA dons new clothes. 1998. *Nature Biotechnology* 16

**C. *Potential Transfer of Antibiotic Resistance Marker Genes to Gut Micro-organisms***

The second paragraph states:

“In addition, when any DNA (including antibiotic resistance genes) is integrated into plant genomes, the codon usage may have been altered for the more efficient expression in the plant and the gene may have picked up methylation patterns of the plant.”

Codon changes may be silent, but can also lead to phenotypic changes. Whereas this may lead to loss of an antibiotic resistance phenotype if the bacterial gene is recovered from a transgenic plant and is then expressed, this is not, however, always the case. The bla<sub>TEM</sub> gene has been used in the construction of some transgenic plants. The parental gene encodes a narrow spectrum b-lactamase that confers resistance to penicillins such as ampicillin and to certain of the older cephalosporins. The gene encoding this β-lactamase undergoes mutations that alter its active site, the consequence of which is to extend the spectrum of activity of the enzyme. This leads to a phenotype that includes resistance to the newer cephalosporins; drugs that are commonly used to treat life-threatening Gram-negative infections. Alternatively, mutations in this gene mean that enzyme is no longer susceptible to inhibition by agents such as clavulanic acid, used to overcome the resistance phenotype. If passage of the bla<sub>TEM</sub> gene through a transgenic plant leads to alteration of the codon usage, as acknowledged in the document, then the possibility that the phenotype may be extended should also be considered. Paragraph eight goes on to say:

“Other experts would include the beta-lactamase gene of pUC18 (that confers resistance to a narrow spectrum of beta-lactam antibiotics).....”

If it is accepted that codon changes follow the introduction of an antibiotic resistance marker into a transgenic plant, then it must also be accepted that the bla<sub>TEM</sub> gene can mutate to an extended-spectrum β-lactamase phenotype.

The third paragraph states:

“Nonetheless, the possibility was raised that unlikely events could take place given sufficient selective pressure and that, because of the short generation times of bacteria, clonal expansion of the transformed bacteria could take place. For these reasons, and because some antibiotics are so important clinically, it is prudent for developers to ensure that markers genes that encode resistance to clinically important antibiotics are not present in food or feed derived from new plant varieties.”



The ACNFP strongly supports this position. It considers however, that the list should be expanded to include chloramphenicol and amikacin. Ideally a timetable could be set to limit the use of antibiotic marker genes or to excise them from the finished plant before release into the environment.

#### Notes

(5) "The pUC19 *beta*-lactamase gene typically seen in recombinant plant genomes under the control of a bacterial promoter would not pose a health hazard should it be transferred and expressed. Unlike the *beta*-lactamase genes that confer resistance not only to a wide variety of *beta*-lactam antibiotics but also to beta-lactamase inhibitors that have been used to "recycle" antibiotics (e.g. ampicillin) and are currently causing problems in hospitals, this *beta*-lactamase poses no clinical problems because there are many antibiotic formulations that easily control bacterial strains producing it (Salyers, 1996)."

This *beta*-lactamase *is* the progenitor of extended-spectrum *beta*-lactamase and of inhibitor resistant *beta*-lactamase (See <http://www.lahey.org/studies/webt.htm>).

#### E. *Approaches to Assessing Potential for Transfer of Antibiotic Resistance Marker Genes and Conducting Surveillance for Resistance*

##### Paragraph one

In the discussion on transformation, there is a suggestion from certain experts that if *Escherichia coli* does not transform then the results would suggest that such transfer may not take place in natural setting to the extent that they would raise health or safety concerns. The view of the ACNFP is that *E. coli* is an inappropriate organism for this experiment, since it does not readily transform unless conditions are manipulated. *Streptococcus pneumoniae* was the first bacterium in which natural transformation was observed. Members of the family Neisseriaceae are also naturally competent and much more likely to transform than *E. coli*. The family Neisseriaceae includes the significant human pathogens *Neisseria meningitidis* and *Neisseria gonorrhoeae*: the causes of meningococcal meningitis and gonorrhoea respectively. Furthermore, there has now been a demonstration that the microflora in the mouth rumen is capable of natural transformation: the uptake and expression of naked DNA by bacteria. (Flint, H. J.; *Applied and Environmental microbiology: in printing*)

The fourth paragraph states:

"Some experts also suggested that FDA might consider requiring crop developers to monitor for the spread of resistance due to use of an antibiotic resistance marker in a transgenic plant, especially if the gene confers resistance to a clinically important antibiotic. However, it would be a difficult task to document transfer due to the high levels of resistance that already exist."

This may not be such a problem with plants carrying the bla<sub>TEM</sub> gene from a pUC-vector. This gene has been engineered and no longer contains a site recognised by restriction endonuclease *Pst* I found in the wild-type gene. PCR amplification, followed by restriction fragment length polymorphism studies could easily detect the gene from transgenic plants: offering the facility to track such genes through populations. Any such study should of course be backed up by selective culture; to demonstrate the functionality of the resistance determinant. This illustrates that follow-up studies may play a significant role following the commercial release of transgenic plants.

As well as monitoring the movement of resistance genes from transgenic plants, there is the parallel concern that *any* food may act as a vector of bacteria that carry antibiotic resistance determinants. These may have the potential to pass resistance onto the human flora following

consumption of the "contaminated" food. The ACNFP would urge a baseline study to see what contribution this makes to the spread of resistance in significant human pathogens.

## II. Issues Considered by the FDA

### C. Potential Transfer of the Kanamycin Resistance Gene

#### 2. Potential transfer of the kanamycin resistance gene to soil micro-organisms

It is suggested in this section that transfer of resistance marker genes to soil organisms would be unlikely. Given the huge amplification of resistance genes implicit in the agricultural application of transgene technology, even rare events *will* happen. Furthermore, recent work at the University of Leeds has demonstrated the relative difficulty with which plant DNA is degraded during food processing. (Report will be available shortly from: MAFF Library, Nobel House, 17 Smith Square, London SW1P 3JR) This research indicates that there is cause to be concerned about the problem of gene transfer to environmental organisms. Such bacteria could also act as a gene pool that may interact with human pathogens.

The ACNFP believes that the scope of the document should be broadened to consider issues that it does not address at the moment. For example, the question of whether the widespread use of transgenic plants that carry antibiotic resistance determinants might offer novel routes for the introduction of resistance genes into the microflora needs to be considered. Neither of the terms "gut flora" or "the environment" is defined, but the impression is given that the primary concern of the author(s) has been the facultative anaerobic flora found in the bowel. The gut starts at the mouth, a site noted for its rich microflora; this does not seem to be acknowledged. Another assumption that seems implicit in this document is that the world is populated with healthy adults. Transfer of resistance genes may pose a much more significant threat to the very young, the elderly and those people who are immunocompromised. Exposure of the microflora of these individuals, coupled with the small risk of transfer of a resistance marker, may have much more serious consequences than similar events in healthy adults.

The widespread use of transgenics carrying antibiotic resistance marker genes will involve a massive amplification of these genes in the biosphere. Whether or not these genes are expressed, amplification on the scale that will occur when transgenic crops are planted in large fields means that arguments about the rarity of possible transfer events will become less significant.

There is also a concern that the processing of transgenic plants containing antibiotic resistance marker genes may expose bacteria that have not had prior exposure to these genes. An example may be the exposure of respiratory commensals to the *bla* gene, encoding ampicillin resistance, when humans are exposed to dust (produced during processing) and pollen from transgenic plants containing this gene. The human respiratory flora contains notable potential pathogens including *Neisseria meningitidis* and *Streptococcus pneumoniae*. These bacteria do not currently exhibit high-level, *beta*-lactamase mediated resistance to penicillins.

#### An observation of the use of antibiotic resistance markers in general

The use of a kanamycin resistance marker in transgenic plants is now well established. The arguments in favour of its use are accepted and there is little worry about constructs that exploit this gene. The use of other antibiotic resistance markers in transgenic plants should be vigorously resisted. Even "old" antibiotics that are currently little used may be needed once more if significant problems with resistance to new agents increase. Chloramphenicol was once the first-line treatment for bacterial meningitis. Extended-spectrum *beta*-lactamase are widely used in this role. The *bla* gene may be ubiquitous in the facultative flora of the bowel, but it is not elsewhere. Antimicrobial

chemotherapy has been one of the greatest triumphs of this century. It would be a tragedy if we threw away this gift as we approach the millennium.

I hope that you find these comments constructive.

Yours sincerely

Mr N Tomlinson  
Additives and Novel Foods, Branch 'C'  
**MAFF**

# Appendix XII

## Health and environmental risks of genetically modified soya: food safety issues considered by the ACNFP

### FOOD SAFETY ISSUES CONSIDERED BY THE ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

#### Background

1. In 1994, the Advisory Committee on Novel Foods and Processes (ACNFP) reviewed the food safety of genetically modified (GM) soya beans and derived products developed by Monsanto. The Committee recommended safety clearance for the glyphosate tolerant line 40-3-2, which had been modified to contain the epsps gene, and its descendants from crosses with non-GM lines produced through conventional plant breeding. The Committee's report was published in its 1994 Annual Report and the information submitted by Monsanto was deposited in the British Library.
2. In December 1997, the ACNFP was asked to consider a paper that was submitted to the Minister of State by Greenpeace. In the paper, Greenpeace described the granting of a marketing consent for line 40-3-2 as "regulatory negligence". Points presented in Greenpeace's paper of relevance to the ACNFP's consideration of the food safety of this line are discussed in the sequence presented in the paper.

#### SAFETY ASSESSMENT

##### *Accusation: Monsanto had submitted no toxicological assessments*

3. Wherever possible, the ACNFP uses a comparative approach to establish the safety of a novel food. This requires the novel food to be compared with a conventional equivalent; usually in the case of a genetically modified organism (GMO) this is with its non-GM parent. In the first instance, compositional data relating to nutritional and toxicological parameters are compared. Should concerns be identified, further studies will be requested. With the introduction of the Novel Foods Regulation, this approach has been formalised throughout the EU in the application of the concept of "substantial equivalence".
4. The ACNFP concluded that the GM soya beans were safe after its rigorous examination of the detailed compositional and nutritional data that had been submitted. The Committee was satisfied from the evidence provided that the GM soya beans were as safe as conventional beans and that additional toxicological studies would not be necessary.

##### *Accusation: Monsanto had submitted no independent verification of its conclusions and no peer review of its methodology*

5. The ACNFP has always required that data submitted for assessment is to Good Laboratory Practice (GLP) standards. Monsanto submitted data that had been quality assured to these standards. Under GLP all studies must follow written standard procedures and all laboratory records and samples must be archived. All laboratory facilities are inspected by independent inspectors.

6. The ACNFP's approach, based on the comparison of a GM food with its traditional counterpart has been subject to wide consultation, most recently when the Committee revised its structured schemes. The application of the concept of substantial equivalence, a concept that was developed by the WTO, has been subject to extensive peer review.

***Accusation: Genetic drift***

7. Genetic stability is a key aspect of the ACNFP's safety consideration. Indeed because there is currently little expertise in predicting the effect of genetic drift on the metabolism of any lines of plants, whether GM or conventionally bred, the ACNFP requires all applicants to provide periodic updates to substantiate the long term stability of GM lines.

***Accusation: Data obtained from soya that had not been treated with glyphosate***

8. The ACNFP was satisfied that the composition of the GM soya was equivalent to that of non-GM soya and that there were no unintended effects as a result of the genetic modification. Data on soya treated with glyphosate was reviewed by the ACNFP and other EU competent authorities and raised no concerns.

**ALLERGENICITY**

9. Monsanto carried out an immunoblot assay on the GM soya beans, their non-GM parental line and three commercially available soya flour preparations. This assay is routinely used in the assessment of soya bean allergens and involves detection using IgE antibodies derived from serum from individuals known to be sensitive to soya beans through direct food challenges. The presence and relative levels of endogenous allergenic proteins in all of the preparations were comparable.
10. In addition, the CP4 EPSPS protein, which is produced by the introduced gene, was extensively tested. It was shown to be inactivated and denatured by heating, rapidly inactivated by mammalian digestive fluids, unglycosylated and database searches showed no significant homology to any protein allergens.

**ANIMAL FEEDS**

***Denaturation of the EPSPS protein by heat treatment***

11. Monsanto supplied data to demonstrate that all detectable functional activity and ELISA reactivity of the EPSPS protein was lost following the toasting procedure used to process soya beans. Although a portion of the protein mass was still detectable by immunoblot assay after the heat treatment, the tests indicated that the tertiary structure had been altered; the protein molecule was denatured and was no longer functional.
12. As discussed in (8) Monsanto had provided evidence to demonstrate that the EPSPS protein is not allergenic.

***History of safe use***

13. As part of the conditions of clearance of the GM soya bean, Monsanto undertook to review compositional data to ensure that the GM beans remained genetically stable. The first of these reports have been received which indicate that there no significant differences between the GM soya beans and the non-GM lines analysed.

***Accusation: Allergic reactions to foods in adults with no history of food allergies***

14. The ACNFP was satisfied that Monsanto had demonstrated that the presence and relative levels of endogenous allergenic proteins in preparations of GM and non-GM soya beans were comparable.

#### **ENVIRONMENTAL EFFECTS**

15. The issues regarding environmental safety were addressed by the Advisory Committee on Releases to the Environment (ACRE) when assessing the application for a marketing consent under the Deliberate Release Directive 90/220/EEC. Since the GM soya was not intended for cultivation in the UK or Europe, the issues raised by Greenpeace regarding the changes in herbicide usage do not fall within the remit of the ACNFP.

#### **Conclusions**

16. The ACNFP rejects the Greenpeace allegation of regulatory negligence and reiterates its original conclusion that beans and derived products from GM line 40-3-2, and from its descendants from crosses with non-GM lines produced through conventional plant breeding, were as safe for human consumption as beans derived from other conventional soya bean lines.

# Appendix XIII

## ACNFP response to the Greenpeace report 'Genetic Engineering, too good to go wrong'

### ACNFP CONSIDERATION OF GREENPEACE REPORT ON GENETIC MODIFICATION

#### SUMMARY

Overall the ACNFP considers that the examples cited by Greenpeace demonstrate that the regulatory process is robust and readily identifies any untoward effects. Whilst making a strong case for continued vigilance the Greenpeace report provides no justification for changes to the current regulatory framework.

#### INTRODUCTION

1. The Greenpeace report written by Dr Parr entitled 'Genetic engineering: too good to go wrong' was sent to all ACNFP members by post. This response represents their collective views. Whilst the ACNFP's remit focuses on the food safety implications of GMOs, members were invited to comment on all aspects of the report.
2. The Greenpeace report consists of an introduction setting out the reasons why Greenpeace is opposed to the introduction of GM0s. This is followed by 12 case studies that are intended to underline the Greenpeace arguments about the unpredictable nature of GMOs.
3. In his introduction, Dr Parr suggests that 'science cannot make genetic engineering safe'. He then goes on to suggest that 'what is an acceptable risk is a matter of opinion – a matter of judgement not a technical question?' However, crop improvement via conventional breeding, involving the utilisation of wild relatives and even different species in breeding programmes, introduces risk of insertional events, introduces large amounts of DNA, the effects of which in the food chain are not known, as well as many of the other possible hazards Greenpeace have discussed for GMOs.

Thus the question arises, is the genetic modification of crops more or less hazardous than conventional breeding? It can be argued that GM crops are less hazardous because:

- (1) we can define what is put in, in terms of the DNA sequence and we have some knowledge of where it goes;
- (2) the GMOs receive much greater levels of testing than the conventional varieties.

The important point is that the focus should be on the products *per se* and their risk rather than on the technology used to produce them.

4. The report suggests that the agricultural applications of GMOs involves the 'irreversible and uncontainable' release of GMOs to the environment. In practice most crop plants, whether they have been genetically modified or not, do not survive in the wild, this is particularly true of most cereals grown in the world today.
5. The report criticises the commonly quoted justifications for crop biotechnology. However, there is no mention of the fact that there are many millions of people alive today who would not have survived were it not for the massive improvements in crop yields brought

about by the development of new agricultural technologies. Inevitably ensuring that food supplies keep pace with the growth in world population will involve a variety of other factors. However, keeping crop yields pegged at today's levels is not an option.

## THE TWELVE CASE STUDIES

6. The report cites 12 case studies to justify the assertion that genetic modification is so unpredictable that it should not be permitted. However, the key question is whether the European regulatory framework is robust enough to deal with such incidents. Each case study is considered briefly below.

### Case 1

*Accusation: Microbes that don't behave as predicted*

The European regulatory system requires monitoring of trial sites during and following experimental releases. In the UK, the HSE inspects trial sites to ensure conditions of consents are complied with. There is some doubt about the conditions of the experiment referred to in this case study. Biotechnica International are known to add nutrient media to the soil as part of their experiments. There is no indication that any harm occurred as a result of the trial.

### Case 2

*Accusation: Mix-up of genes provokes costly recall*

The reference to Monsanto's oilseed rape refers to two very similar lines of oilseed rape. In Europe, no seed, GM or conventional, can be grown commercially unless it appears on the Common Catalogue. Before seed is listed on the Common Catalogue, it must be shown to have a value for cultivation and be distinct, uniform and stable.

### Case 3

*Accusation: Gene changes create unanticipated allergies*

The potential allergenicity of proteins expressed by novel genes is addressed as part of the safety assessment process. The Pioneer soya bean example demonstrates the effectiveness of existing controls.

However MAFF and other organisations are funding research to further refine methods for predicting the allergenic potential of proteins.

### Case 4

*Accusation: Bacteria poison soil*

Ethanol is used to kill microbes, it is hardly surprising that a bacterium producing excess ethanol affected the local microflora adversely. From the report it is not clear whether this experiment was carried out as a field trial or in a laboratory.

### Case 5

*Accusation: Animal health problems from extra growth hormone*

The examples relating to the use of growth hormones have been rightly criticised for the unnecessary suffering inflicted on the animals involved. The controls imposed by the Animal Scientific Procedures Act ensure that animal welfare is given a higher priority in the UK.



## Case 6

*Accusation: Toxic by-products kill beneficial soil life*

It is not clear whether the example quoted refers to a field trial or laboratory experiment. Certainly the fact that 2, 4-DCP was toxic is not altogether surprising.

## Case 7

*Accusation: Laboratory costs spread unpredicted contamination*

It is not clear whether the Dutch study cited involved GM or non-GM bacteria. The Greenpeace report suggests that there is a risk of contaminated laboratory coats acting as a vector for the spread of GM micro-organisms into domestic sewerage systems. However the contamination of lab coats is covered as part of the standard risk assessment required under the contained use regulations. Indeed it is standard practice to autoclave such coats before they are laundered.

## Case 8

*Accusation: Toxic products from engineered yeast*

There is nothing very surprising with this example. Yeasts and other microorganisms are modified to alter metabolic pathways with the build up of a specific metabolite frequently being the intended end result. Where such organisms are intended for food use careful consideration is given to the possibility that levels of toxic metabolites might have been increased. This example again illustrates the effectiveness of existing safety assessment procedures in identifying such cases. It is interesting that much is made of the fact that this yeast produced elevated levels of methyl glyoxal, a compound that occurs widely in foods and beverages and has some mutagenic activity *in-vitro*, although of course yeast is also well known for producing significant quantities of ethanol.

The International Agency for Research on Cancer (IARC) does not consider methyl glyoxal classifiable with respect to carcinogenicity but does consider drinking alcoholic beverages to be a clear cause of human cancer. The Committee on Carcinogenicity (COC) concluded that the risk of cancer associated with drinking alcoholic beverages was due to the consumption of ethanol.

## Case 9

*Accusation: Did genetic engineering produce a deadly food supplement?*

The Tryptophan case has been studied in great detail. It is of considerable interest to groups such as Greenpeace in that it is probably the only example where any serious adverse effects can be even indirectly attributed to a GMO. However, a closer examination of the facts reveals that the cause of the deaths associated with tryptophan had less to do with the source organism and more to do with a failure in quality control procedures. In this particular case the company had removed 3 key stages from the past production purification process including a crucial carbon filtration. The tryptophan incident illustrates the need for companies to put in place robust quality control procedures.

This is an issue that the ACNFP attaches great importance to and information on such procedures forms an essential part of the ACNFP's safety assessment process.

**Case 10**

*Accusation: Weather changes gene expression*

As indicated in the response to case 2, a requirement for entry onto the Common Catalogue is that a new variety must be shown to be stable. Although colour fading of flower petals on prolonged exposure to light is a phenomenon observed in most flowers.

**Case 11**

*Accusation: Transplanting seedlings changes gene expression*

This case illustrates the importance of ensuring that novel genes are stably integrated into the plant genome. This is a key aspect of the ACNFP's consideration. Indeed because there is currently little experience in predicting the effect of genetic drift on the metabolism of any lines of plants whether genetically modified or conventionally bred the ACNFP requires all applicants to provide periodic updates to substantiate the long term stability of GM Lines. Again the particular example quoted shows no evidence of harm, indeed loss of the herbicide tolerance trait is self limiting.

**Case 12**

*Accusation: Failed tomato shows 'real world' uncertainties*

This example has nothing to do with the safety or otherwise of GM tomatoes. It is an example of how companies need to consider the commercial implications when developing any new product

**CONCLUSIONS**

7. The Greenpeace report serves a useful purpose in demonstrating the need for continued vigilance by regulatory authorities. However, there is no sustainable justification in the report for a ban on the release of all GMOs into the environment. The report indirectly highlights the strength of the existing European regulatory framework in being able to ensure that activities involving GMOs do not cause harm to human health or the environment in Europe.

# Cumulative index

Topic	Report	Page
Amylolytic yeast	1993	4
	1992	16
Antibiotic resistance markers	1998	12
	1995	18
	1994	3
	1993	13
	1991	17
	1990	10
<i>Bacillus laterosporus</i>	1994	7
	1993	7
Bakers yeast – genetically modified	1990	2
	1989	
Camelina Oil	1998	10
Cereal Fractions	1998	6
Chaparral	1993	6
Cherry and apricot kernel oils	1993	10
	1992	12
Chicory – GM	1998	8
	1996	12
Chymosin – Ex <i>E coli</i>	1992	9
	1991	10
– ex <i>Asp niger var awamori</i>	1990	3
– ex <i>K lactis</i> 19903 from GM source	1989	6
Code of Conduct	1998	28
COMA/ ACNFP ad hoc joint Working group	1998	11
Consumer concerns – workshop	1991	16
	1990	10
COT – joint meeting	1998	13
	1991	15
Cottonseed – genetically modified for herbicide tolerance	1998	6
	1997	12
	1996	5

Topic	Report	Page
Cottonseed – genetically modified for insect resistance	1998	6
	1997	11
Culture collections	1995	18
Dextrans – in fructose syrup	1990	3
	1989	6
– in clinical nutrition products	1993	6
EC Regulation on Novel Foods	1998	1
	1997	3
	1996	19
	1995	19
	1994	11
	1993	15
	1992	21
Education in biotechnology	1991	18
<i>Enterococcus faecium</i>	1995	3
Enzyme hydrolysis of whole grain	1991	6
	1990	5
Enzymic modification of vegetable oils	1995	11
	1993	4,5
	1992	10
	1991	12
	1990	5
Fruitrim	1998	10
Gene transfer – MAFF research	1998	12
Germanium	1991	11
GLA oil	1991	8
	1989	8
Greenpeace Report – ACNFP Response	1998	13
Green Tea Extract	1996	15
	1995	15
Guarana	1996	16
	1995	16
	1993	8
Guidelines on testing	1991	6
	1990	9
	1989	9

Topic	Report	Page
HAZOP – structured approach to assessment	1994	10
	1993	12
	1992	18
Health and Environmental risks of GM soya: Food safety issues considered by ACNFP	1998	13
Hemicellulase enzymes – from GM sources	1997	10
	1996	12
	1995	12
Interesterified fats for infant formulae	1995	16
	1993	11
	1992	17
Irradiation – polyploidy	1989	3
– X-ray surveillance equipment	1990	6
– 24 hour rule	1990	6
– neutron surveillance devices	1992	13
– detection tests	1992	19
EC Directive	1998	15
	1997	16
	1996	19
	1995	19
	1994	11
Joint meeting with the COT	1997	14
Labelling – products from genetically modified sources	1998	15
	1997	16
	1993	13
Lactobacillus GG	1993	10
	1992	12
Lipase ex <i>Asp oryzae</i>	1995	14
	1994	7
	1992	17
Low $\alpha$ -linolenic form of linseed	1997	8
Lupins/lupin fibre	1996	14
	1995	10
	1992	15
	1991	13
	1990	9
Long-chain polyunsaturated fatty acids for use in infant formulas	1997	8
	1996	9
	1995	14

<b>Topic</b>	<b>Report</b>	<b>Page</b>
Maize – genetically modified for insect resistance	1997	10,12
	1996	6,16
	1995	7
Maize – gentically modified for herbicide resistance	1997	11
	1996	4
Members' interests	1998	25-28
	1997	26-28
	1996	28-30
	1995	28-30
	1994	23-25
	1993	25-27
Novel fat replacer – structured triglycerides composed of mixtures of short & long-chain fatty acids	1997	8
	1996	11
	1995	15
	1989	7
	1994	8
	1992	16
Novel foods	1996	18
Novel foods for Infants	1998	11
Nutritional implications	1997	14
	1993	12
	1992	18
Ohmic heating	1995	10
	1992	8
	1991	8
	1990	8
Oil from GM oilseed rape	1995	3,5,6
	1994	4
– oil with high lauric acid content	1996	12
OECD Meeting	1994	12
	1993	16
Passion fruit seed oil	1991	7
	1990	4
Pine Bark Extract	1997	9
Phospholipids from Egg Yolk	1998	9
Pollen from GM plants in honey	1992	11
	1991	13
	1990	9

Topic	Report	Page
Polyporus squamosus – mycelial protein	1993	8
Polysaccharide fat replacers	1997	9
Post market monitoring of novel Foods – ACNFP sub group	1998	14
Potatoes genetically modified for insect resistance	1997	12
GM Potato Research at Rowett Institute	1998	12
Quinoa	1995	16
	1992	15
	1991	13
	1990	8
Riboflavin from GM <i>Bacillus subtilis</i>	1996	7
Risk assessment: role of Advisory Committees	1998	11
Royal Society statement on GM Plants for food use	1998	12
Single cell protein	1997	10
	1996	12
Enzymatically partially depolymerised polysaccharide	1996	11
	1995	15
Soya beans – herbicide resistant	1994	5
Statistically valid data to support Safety clearance of crops products	1998	10
<i>Stevia Rebaudiana</i> Bertoni	1998	8
Substantial Equivalence	1998	1
Sugar beet fibre	1992	17
Taste trials – guidelines	1992	9
	1991	10
– beers from GM yeasts	1990	2
	1989	5
– GM tomatoes	1990	5
Processed products from GM tomatoes	1997	7
	1995	9
	1994	3
GM Tomatoes to be eaten fresh	1995	8
Toxicological assessment of Novel foods	1998	11

<b>Topic</b>	<b>Report</b>	<b>Page</b>
Transgenic animals	1994	9
	1992	7
	1991	7
	1990	7
	1989	8
	1993	9
– ethics group		
Transparency of the ACNFP	1998	14
	1997	14
Trehalose	1991	8
	1990	4
US Food and Drugs Administration paper on antibiotic resistance markers	1998	12
WHO workshop	1994	12





MAFF Publications  
ADMAIL 6000  
London SW1A 2XX  
© Crown copyright 1999  
PB 4393