ACNFP Advisory Committee on Novel Foods and Processes

Annual Report 1999

Ministry of Agriculture, Fisheries and Food

Department of Health

ACNFP Advisory Committee on Novel Foods and Processes

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

'to advise the central authorities responsible, in England, Scotland, Wales and Northern Ireland respectively on any matters relating to novel foods and novel food processes including food irradiation, having regard where appropriate to the views of relevant expert bodies.'

Contents

Foreword		υ
Introductio	n	vi
1.	The EC Novel Foods Regulation (258/97) 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	1
2.	Full applications submitted to the UK Competent Authority Cereal fractions Salatrims Processed products derived from GM tomatoes	4
3.	Substantial equivalence applications submitted to the UK Competent Authority Herbicide tolerant cottonseed Insect resistant cottonseed Herbicide tolerant oilseed rape	7
4.	Applications submitted to other Member States Phytosterol esters (Netherlands) Phospholipids from egg yolk (Belgium) <i>Stevia rebaudiana</i> Bertoni (Belgium) GM <i>Radicchio rosso</i> and green hearted chicory (Netherlands) Nangai (Ngali) nuts (France) PrimaDex – Bacterial Dextran (Belgium)	8
5.	Other issues considered by the ACNFP Decisions on Novel Food status: Lyprinol Calcium-L-Mefolinate	12
	 Reports and other issues Benecol Draft guidelines on the use of human volunteer studies in the pre-market safety assessment of novel foods COT review of Dr Pusztai's research on GM potatoes Gene transfer (IVEM report) Crossing of two GM plants Joint ACNFP/ACAF meeting Seminar on allergenicity (March 1999) Seminar on novel techniques for the analysis of GM foods (November 1999) 	13

Page

6.	Other activities Increasing the openness of the ACNFP ACNFP Sub-Group on post market monitoring				
7.	Developments elsewhere EC Directives on food irradiation Labelling of GM foods				
8.	Contact points				
9.	References				
10.	Glossary				
11.	Appendices				
	Ι	ACNFP – remit, membership and list of members' interests, code of conduct and interaction with other committees.	27		
	Π	UK Competent Authority initial assessment report on the safety of soluble and insoluble fractions of cereal brans, for use as fat replacers and sources of dietary fibre: final report sent to the European Commission.	38		
	III	UK Competent Authority initial assessment report on the safety of Salatrims – a family of reduced calorie fat replacers: final report sent to the European Commission.	46		
	IV	Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to Phytosterol esters.	66		
	V	Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to Nangai nuts (<i>Canerium indicum</i> L).	68		
	VI	Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to PrimaDex – High Molecular Weight Bacterial Dextran.	70		
	VII	Letter from the Department of Health to health professionals regarding phytosterol esters and phytostanol esters (Benecol).	71		
	VIII	Statement on the studies conducted at the Rowett Research Institute on potatoes genetically modified to produce the snowdrop (<i>Galanthus nivalis</i>) lectin. (Including the COT Statement)	73		
	IX	Minutes of the joint meeting of ACNFP and ACAF: 1 December 1999.	77		
12.	Cumulative index				

Page

Foreword

The contents of the 1999 Annual Report of the Advisory Committee on Novel Foods and Processes indicate the range of activities undertaken by the Committee. Our central function continues to be the assessment of the safety of the novel foods and processes submitted to the UK Competent Authority and to comment upon applications submitted to the competent authorities of other Member States. In order to discharge this function the Committee draws upon the wisdom and knowledge of its Members. Their expertise in science and medicine is world class and we are fortunate that we have representation and advice from members with consumer and ethical backgrounds who are also able to engage in the scientific debate. We are committed to providing an accurate and robust assessment of the data provided in order to formulate advice to government and provide clear and unbiased information to the consumer. In order to do so we must, and do, remain scrupulously independent of government and the industry as we explain the science and participate in the current debate.

It is vital to make the public aware of this rigor and independence as we engage in our deliberations. Therefore we continually strive to increase the transparency with which we operate. Our first move from May 1998 was the publication of our minutes. We have also made available Secretariat reports and reports on evaluations, produced a user-friendly corporate brochure and held a series of open meetings. Since the end of 1999 public participation in the safety assessment process has been extended by the routine requirement for public disclosure of all non–confidential data relating to submissions. This will give interested parties an opportunity to read, and make comments on applications and for these comments to be taken into account by the ACNFP in its evaluation. In addition our draft conclusions will be available for comment. We expect that this will lead to a wider understanding of the Novel Food approval process.

The amendment of the labelling regulations (as described in section 7 of this report) and the establishment of a 1% adventitious threshold for non-GM produce is now in place. Work is ongoing in the EC to determine the negative list of ingredients that do not require labelling.

Transparency of the regulatory process, clear unambiguous and easily understood labelling (with appropriate enforcement regimes), and constant dialogue with consumers, industry, government, the press and broadcast media continue to be essential to ensure that we are able to reap the benefits of novel food technologies. As we move forward we are providing information for individuals to come to their own decisions and make informed choices.

As we continue to strive for greater transparency we are leading the rest of Europe and will continually move forward towards greater openness.

J M Bainbridge O.B.E.

Introduction

This is the eleventh annual report of the work of the Advisory Committee on Novel Foods and Processes (ACNFP). The report begins with an overview of the EC Regulation on Novel Foods and Novel Food Ingredients (258/97) which came into force on 15 May 1997.

The ACNFP received a number of applications in 1999, details of which are at Sections 2, 3 and 4 of this report. Section 2 contains reports of full applications initially received by the UK Competent Authority; Section 3 contains details of applications to the UK for an opinion on substantial equivalence in accordance with article 3(4) of the Novel Food Regulations; and Section 4 contains details of reports on applications made to another Member State, who provided the initial opinion. Those topics discussed during 1999 that were continuations of previous work are indicated as such.

The Committee also discussed a number of general issues during the year, including a review of Dr Pusztai's work on GM potatoes. This can be found at Section 5. Other activities carried out by the Committee in 1999 included the last of a series of open meetings of an ACNFP Sub-Group which considered the post market monitoring of novel foods.

As part of the Committee's commitment to increasing the transparency of its work, with effect from 21 December 1999, it took the unprecedented step of releasing to the public all non-confidential information contained in applications to the UK Competent Authority. Public comments on the applications are invited, and taken into account when the Committee makes its assessment. Further details can be found at Section 6.

A cumulative index of topics considered in previous annual reports can be found at Section 12. Copies of previous annual reports can be obtained from the MAFF Secretary to the Committee (see section 8). The Committee's last two annual reports, as well as other information can be found on it's website at www.maff.gov.uk/food/novel.htm, from 1 April 2000 this will move to the Food Standards Agency website at www.foodstandards.gov.uk.

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 Ingredients¹³, 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, however the Food Standards Agency will take over this function from 1st April 2000.

The Regulation defines a novel food as a food which has no significant history of human consumption within the Community prior to May 1997, 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 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 guidelines¹⁴ (details of which are available from the Stationery Office or the ACNFP Secretariat, see page 22). 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 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 using 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 the 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 applicant must supply evidence that supports its view.

Under article 3 (4) of the Novel Foods and Novel Food Ingredients Regulation (258/97) a simplified procedure exists whereby a company can notify the commission that they intend to place a product in catagories b, d or e (see page 1) on the market. With such a notification the supporting evidence can be based upon the opinion of a Competent Authority or on generally available and recognised scientific evidence. The evidence must show that the novel food or food ingredient is substantially equivalent to an existing food or food ingredient as regards to composition, nutritional value, metabolism, intended use and the level of undesirable substances it contains.

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 report⁸. Those products that were known to have been marketed before May 1997 have been indicated on this list with an asterisk. Copies can be obtained from the ACNFP Secretariat (see page 22).

Under the Novel Foods Regulation, even if a product had been cleared previously 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 another EU Competent Authority but remain, in the UK, subject to the provisions of the Food Safety Act (1990)¹⁵.

2 Full applications submitted to the UK Competent Authority

Cereal fractions

2.1 In 1998 the Committee had been asked to give an opinion on the substantial equivalence of a range of soluble and insoluble polysaccharides derived from cereals – 'cereal fractions' – that were proposed for use as a fat replacement in a variety of manufactured food products. This application had initially been considered under the voluntary system that existed in the UK for consideration of novel foods before the EC Regulation came into effect in May 1997. At that time the Committee had requested that further information be provided on the behaviour of the materials in the gut.

The Committee had been generally satisfied with the data submitted in 1998, but had concluded that the cereal fractions could not be considered to be substantially equivalent to the cereal brans from which they were derived. This was because the isolated fractions might have different physiological actions to the parent materials and because the range of food applications was wider. The Committee recommended that the cereal fractions should undergo a full evaluation under the Novel Food Regulation. The Committee also asked for further supporting data to be submitted on possible adverse gastrointestinal effects and on possible intake, particularly by children (see pages 6–7, section 3.3 of the 1998 Annual Report ¹⁰).

In 1999 a submission was received from Du Pont (UK) Ltd for an opinion from the UK Competent Authority on the acceptability of defined cereal fractions for use as fat replacers and sources of fibre. The Committee considered the application at its May meeting and concluded that it was satisfied with the data provided. In particular there is a detailed specification for the final ingredients and the process by which they are produced is well defined and controlled. Information was provided on the nutritional consequences of using these ingredients in food to partially replace fat or as a fibre source. Based on estimated levels of intake arising from the uses proposed, there was evidence to demonstrate that these ingredients would be fermented relatively slowly in the large bowel, in comparison with starches and pectins. Thus their consumption would not lead to adverse consequences from the fermentation of rapidly released short chain fatty acids, even in the developing gut of children.

The Committee opinion on this application was forwarded to the Commission for consideration by other Member States in June 1999. A copy of this opinion is at Appendix II.

Objections were raised by a number of other Member States and this application has now been referred to the European Commission Scientific Committee for Food (SCF) for an opinion.

At the time of going to press the SCF had not delivered its opinion on these products.

Salatrims

Professor Sanders conducted the thrombogenesis study for this product and so declared a personal interest and was not present for any discussions on this product.

2.2 A submission was received from Danisco (formerly Cultor Food Science) for an opinion on Salatrims, a family of low calorie structured triglycerides composed of mixtures of short chain and long chain fatty acids. Salatrims had originally been considered by the Committee prior to the introduction of the EC Novel Food Regulation in May 1997 and further information had been requested at that time to support their safety-in-use (see 1995 Annual Report⁷, 1996 Annual Report⁸ and the 1997 Annual Report⁹).

This application was considered by the Committee at its meetings in July and September. In coming to an opinion on this application, the Committee sought advice on the toxicological aspects from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. Details can be found in the Committees on Toxicity Mutagenicity Carcinogenicity of Chemicals in Food, Consumer Products and the Environment Annual Report 1999¹¹.

Salatrims are a series of structured triglycerides that have been designed to provide fewer calories than conventional fats. They are manufactured from traditional food sources using existing food processing technologies. Clearance was sought for the use of Salatrims only in a restricted range of food products, namely baked goods and confectionery. Estimated average and extreme intakes of Salatrims in adults arising from such uses, assuming maximum substitution of conventional fats in these products by Salatrims were provided.

Data to support the safety-in-use of Salatrims were provided from a range of animal and human studies. These addressed a number of possible concerns that had been identified in the course of the previous safety evaluation, namely <u>thrombogenic</u> effects, toxicity of the short chain organic acid component of Salatrims, <u>hepatotoxicity</u> and gastro-intestinal tract symptoms. On the basis of the totality of the data now provided, the Committee was satisfied that Salatrims are acceptable for use in the food product categories described in the application, namely baked goods and confectionery. Any extension of the range of use of Salatrims to other food categories would require a further approval.

The Committee noted that there are no specific safety data relating to possible effects of Salatrims in children. However, a recent unpublished UK dietary survey indicated that the food products that Salatrims would be used in are consumed in approximately equivalent amounts by older children and adults. An exception to this is confectionery, where intake is higher in children than in adults.

As a general principle, young children do not need to restrict their energy intake and therefore, on nutritional grounds, foods containing Salatrims should not be aimed at this age group. However, the question of the applicability of any low calorie/low fat food products for this young age group is a generic one, that is not restricted just to consideration of foods containing Salatrims.

The Committee accepted that Salatrims provide fewer calories than conventional fats and recommended that the consumer should be provided, via labelling on the products themselves, with information on the true caloric value of foods containing Salatrims. It was acknowledged that this is in conflict with the provisions of the present Nutrition Labelling Directive and this issue will need to be resolved at European Commission level.

Detailed descriptions of underlined words are contained in the Glossary

The committee opinion on this application was forwarded to the Commission for consideration by other Member States in November 1999. A copy of this opinion is at Appendix III.

Objections were raised by a number of other Member States and this application has now been referred to the European Commission Scientific Committee for Food (SCF) for an opinion.

At the time of going to press the SCF had not delivered its opinion on these products.

Processed products derived from GM tomatoes

2.3 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. Details are provided in the 1995 Annual Report⁷. In 1997, the Committee received a further submission seeking food safety clearance under the Novel Foods Regulation for peeled and <u>comminuted</u> processed tomato products produced from hybrid lines derived from the GM <u>inbred</u> line TGT7–F. The ACNFP had already evaluated and cleared these for the production of tomato paste under the UK's voluntary scheme for safety assessment prior to the EC Novel Foods Regulation (258/97) coming into force in May 1997. 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 Report⁹).

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 derived from these GM tomatoes were on sale in the EU prior to May 1997. The company therefore submitted a full application in 1998 seeking approval to place on the market all processed tomato products derived from line TGT7F.

A description of the modified tomato and a copy of the committee report are contained in the 1998 Annual Report¹⁰. The ACNFP was able to reaffirm its earlier conclusion that the processed tomatoes from the GM tomato line TGT7F were as safe for human consumption as non-GM processed tomato products. However, other Member States raised objections to the initial assessment of the application, and the European Commission requested advice from its Scientific Committee for Food (SCF).

The SCF published its opinion on 23 September 1999 and concluded that from the consumer health point of view, processed foods derived from GM tomatoes that were the subject of this application are as safe as products from conventional fruit. At the time of going to press, the European Commission had not issued a draft decision, in accordance with article 7 of the Novel Foods Regulation, for consideration by Member States.

3 Substantial equivalence applications submitted to the UK Competent Authority

Herbicide tolerant cottonseed

3.1 In 1997 the ACNFP considered a submission received from Monsanto Europe SA seeking an opinion on the substantial equivalence of processed products derived from GM cotton seed modified to produce the protein CP4 enolpyruvylshikimate-3-phosphate (EPSPS), which confers tolerance to the herbicide glyphosate. The initial assessment was described in the 1997 Annual Report⁹. Further data requested by the Committee were received in 1998. Having considered this additional information the Committee expressed concerns regarding the analytical data for the refined oil put forward to demonstrate that neither the modified gene nor its protein product is present in the final oil. Further information was also required to justify the methodology chosen for the compositional analyses of the oil and the statistical analysis regarding the composition of the GM derived oils. The Committee considered additional data provided by the company in 1999 and were not content with the data provided on the DNA and protein analysis of the refined oil, and questioned whether the analyses for the absence of DNA were as rigorous as they could be. There was also concern regarding the apparent statistically significant differences seen in some of the components of the GM derived oils compared to the controls e.g. in the levels of the cyclopropenoid fatty acids. The Committee asked to see evidence that the range of levels seen in the various experiments are within the normal documented ranges for each of the components where a significant difference was seen.

Insect resistant cottonseed

3.2 A submission was received from Monsanto Europe SA in 1997 seeking an opinion on the substantial equivalence of processed products (oils and <u>linters</u>) derived from GM cottonseed that had been modified to be resistant to insects. The initial opinion, which concluded further data was required, is reported in the 1997 Annual Report⁹. Further information considered by the Committee in 1998 stated that the linters were not to be used as such for food but would be used as a source for the production of additives, which is outside of the scope of the Novel Foods Regulation.

The request for an opinion on substantial equivalence was therefore deemed to relate only to oil produced from the GM cottonseed. The Committee had similar concerns with this application as those with the herbicide resistant cottonseed oil and requested the provision of similar information to resolve this matter.

Herbicide tolerant oilseed rape

3.3 The Committee recommended that an approval be issued to Monsanto in January 1996 to market oil derived from GM oilseed rape tolerant to the herbicide glyphosate. The approval, which is reported in the 1995 Annual Report⁷, stipulated that it should be followed by periodic monitoring of the seed and oil composition, to confirm the long term stability of the modification. In 1999, the ACNFP considered the monitoring data provided by Monsanto in accordance with the conditions imposed by the Committee. The Committee looked specifically at the results of the monitoring of the seed composition and fatty acid profile of the oil and was content with the data provided.

Detailed descriptions of underlined words are contained in the Glossary

4 Applications submitted to other Member States

Phytosterol esters (Netherlands)

4.1 In January 1999 the Committee was asked to consider an initial assessment report produced by the Netherlands Competent Authority for approval of yellow fat spreads containing additional phytosterol esters. Phytosterol esters are naturally present at low levels in vegetable oils and in foods derived from such sources. This application sought approval for addition of extra phytosterol esters to yellow fat spreads with the aim of helping to reduce blood cholesterol levels.

The Committee considered particularly the issues raised by the Netherlands Competent Authority, including effects on absorption of carotenes and possible oestrogenic activity. The Committee was reassured by *in vitro* data demonstrating lack of oestrogenic activity and by the lack of adverse effects in a range of toxicological studies, including a two-generation reproduction study, conducted in rats, as well as by the results of clinical studies in human volunteers.

The Committee agreed in particular that the possibility that some of the oils used in the production of the phytosterol ester ingredient might come from approved genetically modified plant sources, did not raise any particular safety concerns. It was noted that such ingredients would be subject to the labelling requirements applicable to any ingredients derived from GM sources.

The Committee also agreed that the consumption of additional phytosterol esters would not have any significant adverse effects on the absorption of the fat-soluble vitamins D, E and K. However, it concluded that there could be an adverse effect on the absorption of carotenoids.

The Committee agreed that the data provided supported the safety in use of this ingredient, as described in the application. However, in the light of data on the effects of phytosterols on carotenoid absorption, the Committee agreed with the opinion of the Netherlands Competent Authority that the approval should be limited in the first instance to a maximum level of addition of 8% w/w. (for example 8g of phytosterol esters per 100g yellow fat spread).

The Committee also welcomed the fact that the company would be carrying out follow-up studies in human volunteers. It agreed that the provision of such additional data would be essential before any decision could be taken to increase the level of addition of phytosterol esters to yellow fat spreads or to widen the range of food products in which this ingredient could be used.

Finally, the Committee agreed that there should be clear labelling of the phytosterol ester ingredient in food products so that the very small number of people with an inborn error in the metabolism of phytosterol esters could avoid such products.

The Committee accepted that food products containing phytosterol esters would be aimed at the particular section of the population that is trying to control its blood cholesterol levels by dietary means. Whilst there was no concern regarding the safety of spreads containing added phytosterol esters for all population groups, there are sections of the population for whom cholesterol lowering diets are not nutritionally desirable, and in whom vitamin A status may not be optimal. Young children have not yet accumulated adequate stores of vitamin A in the liver and are particularly susceptible to any reductions in the intake of vitamin A precursors. Furthermore, reductions in carotenoid intake in lactating women may result in lower vitamin A levels in their milk. The Committee therefore recommended that appropriate information be made available to these sectors of the public. Advice was sought from the Food Advisory Committee on how this advice might be communicated. Initially, it was recommended that advice should be made available via GPs and other health professionals (such as midwives and health visitors), as well as in magazine articles. However, following subsequent consideration of other ingredients claimed to help lower blood cholesterol levels, the Food Advisory Committee then recommended that information should also be provided on the packaging of the food products themselves.

Details can be found on page 8 of the Food Advisory Committee Annual Report 1999^{12.}

The ACNFP also recommended that information regarding the appropriate daily intake of phytosterol ester-containing products should be made available to consumers on the packaging of the product, as well as via health professionals.

The Committee's opinion on this application was forwarded to the European Commission in March 1999. A copy of this opinion is at Appendix IV.

Objections were raised by other Member States to the initial opinion expressed by the Netherlands Competent Authority and this application was referred to the European Commission's Scientific Committee for Food (SCF).

At the time of going to press the SCF had not delivered its opinion on these products.

Phospholipids from egg yolk (Belgium)

4.2 In 1998 the Committee considered an opinion from the Belgian Competent Authority on an application for authorisation of phospholipids obtained from egg yolks as a novel food. A multi-step extraction, fractionation and enzymatic modification process was used to derive a range of phospholipid products from egg yolk. The Belgian Competent Authority had recommended that the phospholipids were acceptable for use in foods where they had been obtained from egg yolk by physical processing but not following the subsequent enzymatic processing (the last step in the production process). The UK had raised a number of concerns about the application (see 1998 Annual Report¹⁰), as had several other Member States, and in March 1999 further data were circulated to Member States to address these concerns.

Having considered the additional data the ACNFP had some remaining concerns about the lack of data on the allergenic potential of the phospholipids given that they may contain traces of egg protein. However, the Committee was content for the product to be cleared provided that a limit for the level of protein was included in the specification for the product and that the product was clearly labelled as produced from egg.

The dossier was also referred to the EU Scientific Committee for Food (SCF) for its advice. On 17 June the SCF agreed with the assessment of the Belgian Competent Authority that the phospholipids derived using physical processing did not raise any safety concerns. However, for the phospholipids synthesised by enzymatic conversion at the end of the process, additional information was needed before a final assessment of their safety as a food ingredient could be given. The Standing Committee for Foodstuffs accepted the advice of the SCF and accepted the draft Commission decision on 21 October 1999, restricting approval to the phospholipids derived using physical processing.

Stevia rebaudiana Bertoni (Belgium)

4.3 In 1998 the ACNFP considered 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 (see 1998 Annual Report¹⁰). The application was referred to the EC Scientific Committee on Food (SCF) and in June 1999 the SCF published its opinion on the safety of *Stevia rebaudiana* Bertoni plants and leaves as a novel food. The SCF concluded that there were no satisfactory data to support the safe use of these products as ingredients of food. A Commission Decision refusing the placing on the market of *Stevia rebaudiana* Bertoni plants and dried leaves as a novel food or novel food ingredient under Regulation (EC) No. 258/97¹³ was agreed at a meeting of the Standing Committee for Foodstuffs on 21 October.

GM Radicchio rosso and green hearted chicory (Netherlands)

4.4 In 1998 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 plants had been genetically modified to make the male plant sterile as part of a hybrid breeding programme. The Committee had previously considered the safety of the GM *Radicchio rosso* under the UK voluntary system and had agreed that further compositional data were required before a final opinion could be reached (see 1996 Annual Report⁸). The UK had therefore objected to a marketing consent for food being issued for these materials under the EC Deliberate Release Directive (90/220/EEC).

The Committee considered that further information received from the company was inadequate as it did not address its concerns regarding possible secondary effects from the genetic modification on phenotype and composition. The Committee also raised concerns regarding the data on whether a marker gene encoding resistance to streptomycin and spectinomycin gene had been transferred into the GM plants as well as the inadequate data put forward to demonstrate that the composition of the GM plants was comparable to non-GM varieties. They also noted that the labelling of the products was not addressed in the application.

As other Member States raised similar concerns the European Commission asked its Scientific Committee for Food (SCF) for an opinion. The company has since provided data addressing the concerns raised by both the UK Competent Authority and other Member States.

At the time of going to press the SCF had not delivered its opinion on these products.

Nangai (Ngali) nuts – Canarium indicum L (France)

4.5 The ACNFP was asked to consider an application made to the French Competent Authority (CA) to determine whether a history of safe use outside the Community provided sufficient reassurance for the safe consumption of Nangai nuts in Europe.

The Committee noted that as other members of the Canarium family are known to contain substances which are intrinsically toxic, giving rise, for example, to contact dermatitis, further toxicity studies should be undertaken.

The Committee also considered that additional data on <u>allergenicity</u> was required before it could deliver an opinion.

Other Member States also raised concerns regarding the need for further toxicological information. The Commission therefore requested advice from its Scientific Committee for Food (SCF) regarding potential health concerns related to food use of the product.

A copy of the letter to the French CA expressing the reservations of the ACNFP is attached at Appendix V.

At the time of going to press the SCF had not delivered its opinion on this application.

PrimaDex – Bacterial Dextran (Belgium)

4.6 The ACNFP was asked to consider an application made to the Belgian Competent Authority (CA) from Puracor NV, Belgium, for the marketing of a High Molecular Weight Bacterial Dextran (PrimaDex). The Belgium CA delivered a favourable opinion after its initial assessment of the product.

Following detailed consideration, the ACNFP agreed with the opinion of the Belgian CA.

The Committee had previously approved two applications involving Dextrans, fructose syrup containing Dextrans (1990 Annual Report²) and Dextrans in clinical nutrition products (1993 Annual Report⁵).

A copy of the letter to the Commission expressing the opinion of the UK Competent Authority is attached in Appendix VI.

Objections were raised by other Member States to the initial assessment for this product and the Commission therefore requested advice from its Scientific Committee for Food (SCF) regarding potential health concerns related to the food use of this product.

At the time of going to press the SCF had not delivered its opinion on this application.

5 Other issues considered by the ACNFP

Decision on Novel Food status

5.1 a) Lyprinol

The Committee considered an enquiry from Bodycare Corporation Pty Limited about the regulatory status of their product "Lyprinol". This is a marine oil derived from the freeze-dried powder of the New Zealand Green Lipped mussel – *Perna canaliculus*. The powder has been on sale under various brand names (e.g. "Seatone") in Europe since 1975. Lyprinol itself has been on the UK market since 1996, marketed as a dietary supplement, and it has been sold in Norway and Sweden since 1997.

Additional information on various aspects, such as consumption levels, was requested from the company who were advised by the ACNFP Secretariat that any opinion that was offered regarding the regulatory status of this product would be solely that of the UK Competent Authority and a definitive decision should be sought from the European Commission.

On the basis of the information received by the Secretariat, it appeared that Lyprinol might fall within the scope of the EC Novel Foods Regulation as the extracted oil itself has a relatively limited history of use as a food, prior to the introduction of the Regulation in May 1997. However, the status of Lyprinol is viewed quite differently in Sweden where it is classified as a medicinal product under the control of the Medical Products Agency.

In the absence of guidance from the Commission regarding the status of this product, the Secretariat invited the Committee to consider whether the consumption of Lyprinol prior to May 1997 would constitute a history of safe food use such that it can be exempt from consideration under the Regulation.

Having considered the data available, the Committee raised concerns regarding the quality of the mussels used for the product and, more specifically, the potential for the contamination of the mussels by <u>protozoal toxins</u>. The Committee also queried the possible alteration to the fatty acid composition of the components resulting from the extraction process. The Committee suggested that more detailed information on the likely intake levels would be required because the oil is sold in a concentrated form, thus increasing exposure levels. Therefore, the Committee concluded that further information concerning quality control during production and fatty acid composition in particular would be required before a decision could be reached.

The Secretariat agreed to write to the company requesting that they address the concerns raised by the members.

b) Calcium-L-Mefolinate

The ACNFP considered information from Seven Seas Limited about the product Calcium-L-Mefolinate and its proposed use as a food supplement. This is the calcium salt of (6S)-5-methyltetrahydrofolic acid which is presented as a form of methyltetrahydrofolate, one of the main folates in food. The ACNFP Secretariat was informed that Calcium-L-Mefolinate is one of two isomeric forms; the L form is a pure, naturally occurring compound and is biologically active; the D form is biologically inactive. In addition, the DL calcium salt of

Detailed descriptions of underlined words are contained in the Glossary

(6S)-5-methyltetrahydrofolic acid is marketed in Italy by BASF as a medicine with the name "Prefolic". The company intended to market the compound in its pure active L form as a food supplement. Seven Seas consider their product to be a salt of a naturally occurring folate which has a history of safe consumption, and as such it should not be considered as a novel food.

The opinion of the ACNFP was sought. The Committee considered that as the calcium salt is not normally consumed in this form and is produced using a novel process, it constitutes a novel food. Under the direction of the Commission, the UK also requested the opinions of other Member States on whether this compound falls within the scope of the Novel Foods Regulation (EC No. 258/97)¹³. This revealed that its status was viewed differently across the EU, with some Member States considering it as a medicine or vitamin.

The Standing Committee for Foodstuffs was therefore invited to consider the matter in accordance with Article 1(3) of the Novel Foods Regulation. Following this consideration, the Commission concluded that an application to market Calcium-L-Mefolinate should be submitted under the Novel Foods Regulation. The Secretariat subsequently informed the company of this decision.

Reports and other issues

5.2 Benecol

Subsequent to the ACNFP consideration of phytosterol esters (see Section 4.1 of this report), the Committee was asked at its meeting in May to consider whether any of the issues raised by that product were also relevant to Benecol, another cholesterol-lowering food ingredient.

Yellow fat spreads containing Benecol (plant stanol esters) were already on sale in Finland prior to May 1997, when the EC Novel Foods Regulation came into effect. The Commission had therefore ruled that Benecol did not come within the definition of a novel food and thus was not caught by the provisions of that Regulation.

The Committee concluded that whilst it did not have any concerns regarding the safety of foods containing Benecol for any population group, it considered that, as for the phytosterol ester product, foods containing this product were not nutritionally appropriate for young children and pregnant and lactating women.

It agreed that appropriate information on these products should be provided to consumers and sought advice from the Food Advisory Committee (FAC) on how this might be achieved. The FAC had originally advised that such information should be provided to consumers via health professionals and through magazine articles. However, following further consideration of this matter, and taking into account the increasing number of products of this type that were likely to come on the market in the near future, the FAC advised that appropriate information should also be provided on the packaging of the food products themselves. Details can be found on page 8 of the FAC 1999 Annual Report.

A letter from the Department of Health was sent to all relevant health professionals, in February 2000, informing them that foods containing phytosterol esters or Benecol would not be nutritionally appropriate for young children and pregnant and lactating women. A copy of this letter is attached at Appendix VII.

5.3 Draft guidelines on the use of human volunteer studies in the pre-market safety assessment of novel foods

The Committee began the process of drawing up guidelines on the use of human studies, in the pre-market safety assessment of novel foods. Taste trials (for which guidelines already exist) and post-marketing surveillance studies (see section 6.2 of this report) were judged to fall outside the scope of this exercise. The European Commission published 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 in 1997¹⁴. However, not all the data requirements are relevant to every novel food and the appropriateness of human studies as part of this overall data package has to be assessed on a case by case basis. Given the wide variety of foods potentially covered by the Novel Foods Regulation it is not possible to draw up a comprehensive list of foods that would require data from human studies. Therefore it was decided that the ACNFP guidelines should outline three examples of where such data are considered appropriate so as to serve as a guide for when human studies are applicable.

The Committee agreed that the guidelines should make clear that there must be defined, scientific justification for conducting human studies on novel foods. The study objectives should also be explicitly stated from the outset and important principles relating to planning the objectives, the design, conduct, analysis, and reporting of the study should be followed, including that such studies should be conducted in accordance with the principles of Good Clinical Practice and Good Laboratory Practice.

As well as the need for clearly defined, scientific justification for conducting human studies on novel foods, the guidelines will also stress the need for careful consideration to be given to the ethical aspects of such studies and the need to seek approval from an Ethics Committee.

The draft guidelines were reconsidered at the 44th meeting of the ACNFP (27 January 2000) and further amendments were suggested. Once the Committee has cleared a final draft of these guidelines, it is the Committee's intention that they be circulated for consultation.

5.4 COT review of Dr Pusztai's research on GM potatoes

The ACNFP reviewed information available on the research carried out by Dr Pusztai and others at the Rowett Research Institute on potatoes genetically modified to express the snowdrop (Galanthus nivalis) lectin. The original study reports were not available to the Committee. As part of this the Committee considered the report of the audit committee commissioned by the Rowett Research Institute to review the studies, a copy of Dr Pusztai's response to the report and the audit committee's response to Dr Pusztai's comments. The Committee also considered a report produced by Biomathematics and Statistics Scotland, on the statistical analysis of the experiments on GM potatoes and some histopathological data on the intestine of rats fed both GM and non-GM potatoes. The ACNFP had requested that these data be referred to the Committee on Toxicity of chemicals in food, consumer products and the environment (COT) for advice on the significance of the histopathological findings. Having considered all the available data and the advice from the COT (who as part of their consideration of the data, took evidence from Dr Ewan, Dr Pusztai's collaborator), the ACNFP concluded that no meaningful conclusions could be drawn from the data made available on the effect of feeding rats GM potatoes expressing the snowdrop lectin. This was because of serious doubts about the design of the studies and the nutritional quality of the potato-supplemented diets that had been used. A copy of the ACNFP's advice, which includes a statement from COT, is attached at Appendix VIII.

Detailed descriptions of underlined words are contained in the Glossary

Most of the data considered by the ACNFP were published later in the year in The Lancet, although some referees who were asked to review the data did not accept it and felt that it should not be published. (Ewen S W B & Pusztai A. Effect of diets containing genetically modified potatoes expressing *Galanthus nivalis* lectin on rat small intestine. The Lancet 1999; 354:1253–4.)

5.5 Gene transfer (IVEM report)

The Committee was provided with a copy of a report by the Institute of Virology and Environmental Microbiology (IVEM), commissioned by the Health and Safety Executive (HSE), looking at gene transfer from GM microorganisms (GMMs). Although the report related to risk assessments carried out under UK Regulations on the contained use of GM microorganisms, the Committee was asked to consider whether there was anything in it which had significant implications for the risk assessment it carried out on novel foods.

The Committee considered that this was a helpful paper but noted that the report focused on the potential for gene transfer in terrestrial and aquatic environments, rather than in the gut or rumen. It also did not address the possible transfer in Gram positive bacteria, and thus it was of limited relevance to novel food safety assessment.

The Committee expressed concern in relation to some of the comments in the report on the potential risks from the use of antibiotic resistance markers, in particular those relating to the ampicillin resistance gene. The Committee, referring to its previous opinion on the use of the ampicillin resistance gene in a GM maize, agreed that this was a matter of concern. The Committee also noted that its previous advice on the ampicillin gene had been misquoted, as this had in fact related to the use of the maize in animal feed and the potential for transfer to animal gut flora.

5.6 Crossing of two GM plants

The ACNFP is routinely consulted by the Advisory Committee on Releases to the Environment (ACRE) on Deliberate Release Directive applications, particularly in relation to molecular biology aspects and their implications, if any, for the food chain arising from the commercial release of a GM variety.

The Committee considered documents received by the ACNFP Secretariat in relation to an application under the Deliberate Release Directive $(90/220)^{27}$ for a maize hybrid derived from the crossing of two previously approved GM lines.

Recognising that this might be the first of many applications for a product derived from the crossing of two GM varieties, Members were asked to consider the information requirements for any such applications.

In the specific case being considered, the applicant had relied heavily on the fact that the two GM parents of the proposed hybrid had already been approved, and so very little information on the new hybrid was provided.

The Committee was of the opinion that it should not be assumed that the hybrid would exhibit the same properties as the parent lines. Therefore any product that was produced from the offspring of such a cross would, at this stage, need to be assessed on a case-by-case basis in the same way as any other product from a GM variety. In particular, the possibility of unintended effects arising from insertion events brought about by the crossing could not be ruled out. The Committee agreed that approval could not currently be based solely on the properties of the parent line.

The Committee reiterated that in all cases a precautionary approach should be adopted. It noted that other countries, such as the USA, where clearance of a GM line also covered further crosses with other approved GM lines.

The Committee considered that it would be very useful to meet with the newly formed Advisory Committee on Animal Feedingstuffs (ACAF) at an early opportunity to discuss approaches to risk assessment.

5.7 Joint ACNFP/ACAF meeting

Accordingly, members of the ACNFP and the Advisory Committee on Animal Feedingstuffs (ACAF) met together for the first time on 1 December 1999. The main issue for discussion was that of assessment procedures, particularly where there are applications made to the Committees that have both animal feed and human food implications. The Committees also considered a draft specification for a proposed research project, investigating the fate of <u>transgenic</u> material in broiler chickens, and discussed plans for future liaison between the Committees. A note of the meeting is attached at Appendix IX.

5.8 Seminar on allergenicity – March 1999

On 18 March 1999 members of the ACNFP met with MAFF officials to review the research developments in the allergenicity of novel foods currently funded by the Ministry. The Committee agreed that the meeting had provided a welcome opportunity to review research in this area. In particular, the Committee noted the potential to utilise human tissues, cells and blood serum for testing the allergencity of novel foods.

5.9 Seminar on novel techniques for the analysis of GM foods

A seminar on molecular methods for the analysis of GM foods was held on 18 November 1999. Members of the ACNFP and other invited experts were briefed by acknowledged experts in various novel techniques (including <u>proteomics</u>, metabolic profiling, and differential displays) and on the latest research developments in their areas of expertise.

The process of assessing novel (including GM) foods needs to be sufficiently comprehensive to be able to address concerns regarding the safety of such foods not only now but also in the future. New technological advances therefore need to be incorporated into the assessment procedure as soon as they are considered to be robust enough to yield meaningful and reliable results.

The members and experts present were asked to consider whether the techniques concerned were robust enough yet for use in the routine safety assessment of novel (including GM) foods. Where they were not, attendees were asked to identify which of them might benefit from further funding to develop their potential to the point where they could be used in this way.

Members considered the workshop to be a very worthwhile exercise. It was felt that the techniques outlined during the seminar could be potentially very useful in helping to characterise more precisely than at present the differences between GM and non GM crops. However, these techniques were considered still to be in their infancy and more research was needed before they could be utilised in the regulatory framework. Delegates were content that current assessments of GM foods are thorough and utilise reliable techniques in order to keep risk to a minimum but that techniques that built on and refined the current assessment would be very welcome once validated. It was felt that, in particular proteomics and metabolic profiling showed sufficient promise to be worth investigating further in the

Detailed descriptions of underlined words are contained in the Glossary

context of crops. To be effective, gene arrays require knowledge of the genome of the target plant and to date only the *Arabidopsis* genome has been sequenced extensively.

A full record of the meeting has been published on the ACNFP website.

6 Other activities

Increasing the openness of the ACNFP

Ongoing measures

6.1 For a number of years the ACNFP has been taking steps to improve the transparency of its safety assessment procedures. During the year the Committee has kept the public informed of its meetings through the advance publication of agendas for discussion and through the publication of minutes of meetings and Secretariat papers presented during its meetings. This information is available on the ACNFP website (www.maff.gov.uk/food/novel.htm) and from the ACNFP Secretariat. Also, the Committee continues to publish reports on its evaluations once the assessment procedures have been completed and encourages companies which make applications through the UK to deposit the accompanying dossier in the British Library.

More generally, in addition to annual reports, the ACNFP produces a corporate brochure which outlines the work of the Committee and its Members. Also, in 1999 there was a further meeting in a series of open meetings, which began in 1998, held by an ACNFP Sub-Group to discuss the feasibility of monitoring novel foods after they have reached the market. Invited observers included Greenpeace, the Consumers Association and representatives from major supermarkets.

New measures in 1999

In 1999 the ACNFP gave a commitment to consider further measures for increasing the involvement of the public and others in its work. To this end new Regulations²⁶ were introduced which, with effect from 21 December 1999, require the routine disclosure for public comment of all non-confidential information provided by companies in support of an application to market a novel food in the UK. These new measures are an amendment to the Novel Foods and Novel Foods Ingredients Regulations 1997,³⁵ introduced to accompany EU Regulation 258/97¹³.

Guidance Notes have been produced which lay down the criteria for deciding what information can legitimately be claimed to be confidential, although the intention is to keep this to a minimum.

In summary, all information included in the application dossier and in any other accompanying documents will be published on the ACNFP internet web pages unless it is:

- (i) information which is not required by the guidelines which accompany the EC Novel Foods Regulation¹⁴; or
- (ii) information which has been agreed by the ACNFP Secretariat to be confidential because disclosure would harm competitive position or Intellectual Property Rights (IPR).

Blanket claims of confidentiality will not be accepted. If the ACNFP Secretariat does not accept the request for confidentiality, the applicant has the option of withdrawing the application, all of which will then be non-disclosable.

The data to be released will be made available to anyone who requests it and will be placed on the ACNFP webpage. Interested parties, including members of the public, will be given 21 days within which to submit relevant comments on the application that the ACNFP can take into account as part of their deliberations. The ACNFP's draft conclusions will also be offered for comment before being finalised, with a period of 10 days within which comments can be made. The Committee recognises that a longer period for comment would be desirable, however, this has to be limited in order for the safety assessment to be completed within the very tight 90 day period allowed by the EC Novel Food Regulation. The new Regulations do not give the ACNFP powers to disclose full details of applications submitted in other EU Member States which are copied to the ACNFP for comment. However, the ACNFP intends to lead the way in Europe by encouraging other Member States to introduce similar measures.

These new measures were subject to a public consultation exercise with draft proposals being sent to some 900 organisations and individuals for comment, as well as being placed on the ACNFP webpage and widely reported in the press. Generally, respondents, including those from industry, were supportive of the concept of increasing the openness of the regulatory process. The Committee hopes that by inviting public participation in the safety assessment process it will increase the wider understanding of the novel food approval process.

ACNFP Sub-Group on post market monitoring

6.2 In response to calls from consumer groups, the ACNFP has been looking at the feasibility of monitoring novel foods after they have reached the market, in order to provide additional reassurance to consumers about the safety of such foods. An ACNFP Sub-Group, which included relevant ACNFP members and experts on health and disease data, met on three occasions to discuss taking the work forward, twice in 1998 and again on 2 September 1999. Invited observers from various organisations, including the major supermarkets, Greenpeace and the Consumers Association, also attended these meetings. The Minutes of these meetings have been published and are available on the ACNFP website.

The ACNFP Sub-Group recommended that before setting up a full scale monitoring system it was essential to test the robustness of data collection procedures through a small scale feasibility study, for which an outline proposal was presented in a paper prepared by an invited expert in this field. Ministers have accepted this recommendation and the commissioning of this feasibility study is under way.

Detailed descriptions of underlined words are contained in the Glossary

7 Developments elsewhere

EC Directives on food irradiation

7.1 The Council and the European Parliament agreed the final text for two Food Irradiation Directives in January 1999 and they were published in the Official Journal of the European Communities on 22 February 1999. All Member States are required to implement the Directives by 20 September 2000.

EC Directive 1999/2/EC¹⁷ is the Framework Directive, which lays down general provisions such as the conditions for treatment, the rules governing the approval and control of irradiation facilities and the labelling of products that have been treated with <u>ionising</u> radiation. EC Directive 1999/3/EC¹⁸ is the Implementing Directive which 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 Directives 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 ACNFP Secretariat (see page 22).

Labelling of GM foods

7.2 EC Regulation 1139/98¹⁹ on the labelling of food and food ingredients containing GM soya and maize (novel DNA or protein), sold to the ultimate consumer, came into force on 1 September 1998. The Food Labelling (Amendment) Regulations²⁰, providing for enforcement of Regulation 1139/98, came into effect on 19 March 1999. The Regulations provide for the manner of marking or labelling of products containing GM soya and maize. They also allow alternative labelling arrangements in respect of foods sold loose, or pre-packed for direct sale, to the ultimate consumer at appropriate premises (this could include food sold from restaurants and bakers). Guidance Notes²¹ explaining the requirements of the legislation were issued in the summer to Local Authorities for distribution to food businesses.

Member States agreed in October 1999 to amend EC Regulation 1139/98. EC Regulation 49/2000²² extends the requirements of Regulation 1139/98 to cover foods sold to mass caterers, and to introduce a 1% threshold for the adventitious contamination of non-GM produce. The aim of the threshold is to ensure that food ingredients obtained from non-GM sources do not need to be labelled as GM if they contain low levels (less than 1%) of GM material as a result of adventitious contamination. The threshold will only apply to ingredients obtained from non-GM sources – there will be no threshold for supplies obtained from sources of unknown origin. Companies should take steps to keep the level of adventitious contamination in non-GM supplies to a minimum and they will also need to be able to demonstrate to enforcement authorities that their ingredients are of non-GM origin.

The 1% threshold is applied at the level of each individual ingredient, and not the final food; therefore the level of GM material in the final food will be much lower.

Detailed descriptions of underlined words are contained in the Glossary

Member States also reached agreement in October 1999 on Commission Regulation $50/2000^{23}$ making foods and food ingredients containing additives and flavourings produced from GMOs subject to the same labelling rules as those of the EC Novel Foods Regulation¹³. The Commission has undertaken to bring forward a proposal to set a <u>de</u> <u>minimis threshold</u> for additives in due course.

The EC Regulations mentioned above come into force on 10 April 2000. A consultation document was issued on 7 January on a draft Statutory Instrument (SI)²⁴ providing for enforcement of these EC Regulations and making continued provision for the enforcement of EC Regulation 1139/98 and the labelling provisions of the EC Novel Foods Regulation. These draft Regulations bring together all the GM and novel foods labelling requirements under one SI. Similar provisions will be made in Wales, Scotland and Northern Ireland.

The European Commission has confirmed that it is working on rules on the use of "GM-free" labelling; and the 'negative list' of highly processed food ingredients where no novel DNA or protein remains, and which therefore do not require labelling.

Further details can be obtained from the ACNFP Secretariat (see page 22).

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 SWIP 3JR

The ACNFP Website can be found at http://www.maff.gov.uk

Information can also be requested via e-mail at: a.acnfp@jfssg.maff.gsi.gov.uk

From the 1 April 2000, the work of the ACNFP will move from MAFF to the Food Standards Agency.

The Agency Website will be found at http://www.foodstandards.gov.uk

Information requests should then be directed to acnfp@foodstandards.gsi.gov.uk

9 References

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- 22. Commission Regulation (EC) No 49/2000 amending Council Regulation (EC) No 1139/98 concerning the compulsory indication on 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* L6 Vol43/13–14, 11 January 2000.
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10 Glossary

allergenicity: the potential or ability to illicit an allergenic response.

caecum/caecal: a blind-ending sac in the digestive system, which in mammals occurs at the junction of the small and large intestine.

carcinogenicity: the potential or ability to cause cancer.

(Hyper)cholesterolaemic: refers to the (elevated) level of cholesterol in the blood.

colonic: of the colon (large intestine).

comminuted: reduced to small fragments.

de minimis threshold: the threshold of 1% for the adventitious contamination of non-GM produce.

fibronolytic: dissolving of blood clots in the circulation.

genotoxicity: an adverse effect on the genome of living cells, which on duplication of the affected cells, the alteration can result in a mutagenic or carcinogenic effect.

hepatotoxicity: degree to which a substance is toxic to the liver.

histopathology/histopathological: microscopic study of the progression of disease in tissues.

hyperplasia: an increase in size of a tissue or organ due to an elevation of the number of cells.

hypertrophy: an increase in the size of a tissue or organ due to the enlargement of individual cells.

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

inocula: micro-organisms introduced into a medium for culture.

interesterification: a reaction between a compound and an ester involving the exchange of alkoxy or acyl groups, resulting in the production of another ester.

Ionising radiation: a form of radiation with sufficient energy to cause an atom to lose or gain one or more electrons leaving it electrically charged. A charged atom is referred to as an ion, hence the term ionising radiation.

lectin: any of a group of plant proteins that bind to specific sugar residues in membrane glycoproteins of animal cells in vitro and cause them to form clumps.

linters: short fibres removed from cotton seeds after ginning.

mineralisation: the process by which the organic components of an organism are replaced by inorganic materials.

mouthfeel: in the context of taste trials for food, the sensation of food in the mouth in terms of it's texture and consistency/substance.

multigeneration study: a study that is performed on subjects from more than one generation of the population. Can be used to trace and predict inherited disease in families.

mutagenicity: the potential or ability to cause mutation.

mycotoxins: toxins produced by fungi, e.g. aflatoxins.

pharmacokinetics: the study of how drugs behave in the body, i.e., how they are absorbed, distributed, broken down and excreted.

plasminogen: the precursor to plasmin, which is an enzyme in the blood that dissolves blood clots.

post-prandial: following a meal.

proteomics: the study of the complement of proteins expressed in a single cell/tissue under specified conditions.

Protozoal toxins: toxins produced by members of the phylum protozoa (unicellular/acellular organisms).

tetragenic: controlled by four genes.

thrombogenic/thrombogenesis: the formation of blood clots.

transgenic: animals or plants which have had genes artificially introduced by genetic engineering.

unsaponifiable: a fat which cannot be hydrolysed by an alkali to form a soap and an alcohol.

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 the central authorities responsible, in England, Scotland, Wales and Northern Ireland respectively on any matters relating to novel foods and novel food processes including food irradiation, 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 (Page 37)

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 1999, together with the names of assessors can 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;
	b) occasional commissions;
	c) share holdings.
Non-personal:	a) fellowships;b) support which does not benefit the member directly e.g. studentships.

Details of the interests held by members during 1999 can be found on page 29.

A copy of the code of conduct for ACNFP members can be found on page 31.

Membership of the committee during 1999

Chairman

Professor Janet Bainbridge O.B.E, BSc, PhD, GradCertEd (Tech), CBiol, FRSA, SOFHT Director, 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 (Retired from the Committee in June 1999) Vice Principal, Heriot-Watt University, Edinburgh

Dr P Dale BSc PhD, CBiol, MIBiol Research Group Leader, Genetic Modification and Risk 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 BA, MA, PhD, PGCE, FIBiol Reader in Education and Bioethics, Homerton College, University of Cambridge

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

Mrs E Russell BSc Consumers Representative

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 C.B.E, FRC Path, FIFST Emeritus Consultant in Microbiology, Guy's & St Thomas' Hospital Trust, London Professor J O Warner MB, ChB, DCH, MRCP, MD, FRCP, MRCPCH, FRCPCH. Professor of Child Health, University of Southampton

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			
Mrs J Whinney	National Assembly for Wales Agriculture Department			
Ms L Wilkie	Scottish Executive Rural Affairs Department			

	Personal Interest		Non-Personal Interest		Partner Interest
Member	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	Ad hoc consultancy	Nestec, Milupa, Nutricia, Wyeth Ajinomoto, FDF, Unilever	Departmental commissioned research and consultancies	None
Dr P Dale	None		European Community United Nations Industrial Development Organisation DETR MAFF/DETR Research	Occasional Advisor Occasional consultant Call-off consultant Seed Samples obtained from various companies	None
			Farm and property seller/purchaser	Advice on Biosafety	
	Personal	Interest	Non-Perso	onal Interest	Partner Interest
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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	Grant from the Gatsby Charitable Foundation	None
Professor I Rowland	Colloids Naturels International (CNI) Rouen, France	Consultancy	Various	Departmental teaching & research funded by various Food companies	None
	Danisco	Consultancy			
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
Dr N Simmons	Food Micro Limited Infection Management Ltd Marks & Spencer plc McDonalds Restaurants Ltd PPP/ Columbia Healthcare Ltd	Director & Shareholder Advisor & Shareholder Independent Advisor Independent Advisor Consultant	None	None	None
	Waitrose Ltd Worshipful Company of Fishmongers	Independent Advisor Bacteriologist			

	Personal	Interest	Non-Pers	onal Interest	Partner Interest
Professor R Walker	Coffee Science Info Centre	Consultancy		None	None
	Numico	Consultancy			
	Colloids	Consultancy			
	Naturel International	,			
	Nestec	Fee			
	Borex Europe Ltd	Consultancy			
	Holland Sweetners	Fee			
	Xyrofin	Fee			
	Tate and Lyle Specialty Sweetners	Fee			
	Hoffman-La- Roche	Fee			
Professor J O	ILSI Europe		SCOPA	Research donations	None
Warner	·		Nutrica (Cow & Gate)	Research donations	
			Various	Research donations	
Professor H F	HSBC	Shareholder	Wide range of	Trustee of the Harry	None
Woods	Halifax	Shareholder	national and	Bottom Charitable	
	Bank		international food	Trust and Special	
			and chemical	Trustees for the	
			companies	former United	
				Sheffield Hospitals	

A code of conduct for members of the Advisory Committee on Novel Foods and Process (ACNFP)

Public service values

The members of the ACNFP must at all times

- observe the highest standards of impartiality, integrity and objectivity in relation to the advice they provide and the management of this Committee;
- be accountable, through Ministers, to Parliament and the public for its activities and for the standard of advice it provides.

The Ministers of the sponsoring departments are answerable to Parliament for the policies and performance of this Committee, including the policy framework within which it operates.

Standards in public life

All Committee members must

- follow the Seven Principles of Public Life set out by the Committee on Standards in Public Life (Page 34);
- comply with this Code, and ensure they understand their duties, rights and responsibilities, and that they are familiar with the function and role of this Committee and any relevant statements of Government policy. If necessary members should consider undertaking relevant training to assist them in carrying out their role;
- not misuse information gained in the course of their public service for personal gain or for political purpose, nor seek to use the opportunity of public service to promote their private interests or those of connected persons, firms, businesses or other organisations; and
- not hold any paid or high-profile unpaid posts in a political party, and not engage in specific political activities on matters directly affecting the work of this Committee. When engaging in other political activities, Committee members should be conscious of their public role and exercise proper discretion. These restrictions do not apply to MPs (in those cases where MPs are eligible to be appointed), to local councillors, or to Peers in relation to their conduct in the House of Lords.

Role of Committee members

Members have collective responsibility for the operation of this Committee. They must:

- engage fully in collective consideration of the issues, taking account of the full range of relevant factors, including any guidance issued by the sponsor department or the responsible Minister;
- in accordance with Government policy on openness, ensure that they adhere to the Code of Practice on Access to Government Information (including prompt responses to public requests for information); agree an Annual Report; and, where practicable and appropriate, provide suitable opportunities to open up the work of the Committee to public scrutiny;
- not divulge any information which is provided to the Committee in confidence;
- ensure that an appropriate response is provided to complaints and other correspondence, if necessary with reference to the sponsor department; and
- ensure that the Committee does not exceed its powers or functions.

Individual members should inform the Chairman (or the Secretariat on his or her behalf) if they are invited to speak in public in their capacity as a Committee member.

Communications between the Committee and the Minister will generally be through the Chairman except where the Committee has agreed that an individual member should act on its behalf. Nevertheless, any member has the right of access to Ministers on any matter which he or she believes raises important issues relating to his or her duties as a Committee member. In such cases the agreement of the rest of the Committee should normally be sought.

Individual members can be removed from office by the Minister if they fail to perform the duties required of them in line with the standards expected in public office.

The role of the Chairman

The Chairman has particular responsibility for providing effective leadership on the issues above. In addition, the Chairman is responsible for:

- ensuring that the Committee meets at appropriate intervals, and that the minutes of meetings and any reports to Ministers accurately record the decisions taken and, where appropriate, the views of individual members;
- representing the views of the Committee to the general public; and
- ensuring that new members are briefed on appointment (and their training needs considered), and providing an assessment of their performance, on request, when members are considered for re-appointment to the Committee or for appointment to the board of some other public body.

Handling conflicts of interests

The purpose of these provisions is to avoid any danger of Committee members being influenced, or appearing to be influenced, by their private interests in the exercise of their public duties. All members should declare any personal or business interest which may, or may be *perceived* (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest which should be declared is on page 35.

(i) Declaration of Interests to the Secretariat

Members of the Committee should inform the Secretariat in writing of their current personal and non-personal interests, when they are appointed, including the principal position(s) held. Only the name of the company and the nature of the interest is required; the amount of any salary etc. need not be disclosed.

Members are asked to inform the Secretariat at any time of any change of their personal interests and will be invited to complete a declaration form once a year. It is 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).

The register of interests should be kept up-to-date and be open to the public.

(ii) Declaration of Interest and Participation at Meetings

Members of the Committee are required to declare any direct interests relating to salaried employment or consultancies, or those of close family members¹, in matters under discussion at each meeting. Having fully explained the nature of their interest the Chairman will, having consulted the other members present, decide whether and to what extent the member should participate in the discussion and determination of the issue. If it is decided that the member should leave the meeting, the Chairman may first allow them to make a statement on the item under discussion.

¹ Close family members include personal partners, parents, children, brothers, sisters and the personal partners of any of these.

Personal liability of Committee members

A Committee member may be personally liable if he or she makes a fraudulent or negligent statement which results in a loss to a third party; or may commit a breach of confidence under common law or a criminal offence under insider dealing legislation, if he or she misuses information gained through their position. However, the Government has indicated that individual members who have acted honestly, reasonably, in good faith and without negligence will not have to meet out of their own personal resources any personal civil liability which is incurred in execution or purported execution of their Committee functions save where the person has acted recklessly. To this effect a formal statement of indemnity has been drawn up.

THE SEVEN PRINCIPLES OF PUBLIC LIFE

Selflessness

Holders of public office should take decisions solely in terms of the public interest. They should not do so in order to gain financial or other material benefits for themselves, their family, or their friends.

Integrity

Holders of public office should not place themselves under any financial or other obligation to outside individuals or organisations that might influence them in the performance of their official duties.

Objectivity

In carrying out public business, including making public appointments, awarding contracts, or recommending individuals for rewards and benefits, holders of public office should make choices on merit.

Accountability

Holders of public office are accountable for their decisions and actions to the public and must submit themselves to whatever scrutiny is appropriate to their office.

Openness

Holders of public office should be as open as possible about all the decisions and actions that they take. They should give reasons for their decisions and restrict information only when the wider public interest clearly demands.

Honesty

Holders of public office have a duty to declare any private interests relating to their public duties and to take steps to resolve any conflicts arising in a way that protects the public interests.

Leadership

Holders of public office should promote and support these principles by leadership and example.

Different types of interest

The following is intended as a guide to the kinds of interests which should be declared. Where members are uncertain as to whether an interest should be declared they should seek guidance from the Secretariat or, where it may concern a particular product which is to be considered at a meeting, from the Chairman at that meeting. **If members have interests not specified in these notes but which they believe could be regarded as influencing their advice they should declare them.** However, neither the members nor the Secretariat are under any obligation to search out links of which they might reasonably not be aware. For example, either through not being aware of all the interests of family members, or of not being aware of links between one company and another.

Personal interests

A personal interest involves the member personally. The main examples are:

- **Consultancies and/or direct employment** any consultancy, directorship, position in or work for the industry or other relevant bodies which attracts regular or occasional payments in cash or kind;
- Fee-Paid Work: any commissioned work for which the member is paid in cash or kind;
- **Shareholdings:** any shareholding or other beneficial interest in shares of industry. This does not include shareholdings through unit trusts or similar arrangements where the member has no influence on financial management;
- **Membership or Affiliation** to clubs or organisations with interests relevant to the work of the Committee.

Non-Personal Interests

A non-personal interest involves payment which benefits a department for which a member is responsible, but is not received by the member personally. The main examples are:

- Fellowships: the holding of a fellowship endowed by industry or other relevant body;
- Support by Industry or other relevant bodies: any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or department e.g.:
 - (i) a grant for the running of a unit or department for which a member is responsible;
 - (ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme in the unit for which a member is responsible (this does not include financial assistance for undergraduate students);
 - (iii) 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, industry or other relevant bodies 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 that industry, the Secretariat can agree with them a summary of non-personal interests rather than draw up a long list of companies. • **Trusteeships:** any investment in industry held by a charity for which a member is a trustee. Where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

Definitions

For the purposes of the ACNFP 'industry' means:

- Companies, partnerships or individuals who are involved with the production, manufacture, packaging, sale, advertising, or supply of food or food processes, subject to the Food Safety Act 1990;
- Trade associations representing companies involved with such products;
- Companies, partnerships or individuals who are directly concerned with research, development or marketing of a food product which is being considered by the Committee.

'Other relevant bodies' refers to organisations with a specific interest in food issues, such as charitable organisations or lobby groups.

In this Code 'the Secretariat' means the Secretariat of the ACNFP.

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 of soluble and insoluble fractions of cereal brans, for use as fat replacers and sources of dietary fibre

Introduction

- 1. In March 1999, an application was received from Du Pont for marketing approval for soluble and insoluble fractions of cereal brans for use as fat replacers and as sources of dietary fibre. The Advisory Committee on Novel Foods and Processes (ACNFP) had previously been asked, in April 1998, for an opinion on the substantial equivalence of these fractions of cereal bran (produced as co-products of an extraction process using aqueous alkali) with the original cereal bran materials from which they are derived. The Committee was of the opinion that the cereal fractions could not be considered to be substantially equivalent to the starting brans from which they had been derived for two reasons:
 - i) they had been isolated from the parent material and thus might have different physiological activities;
 - ii) they were proposed for use as fat replacers, as well as sources of dietary fibre, and thus the applications for use were also different.

The company was informed of the conclusions of the ACNFP and subsequently submitted an application for a full evaluation of these materials under the EC Novel Food and Food Ingredient Regulation. This application is restricted to brans from maize and wheat in the first instance.

- 2. The soluble fraction contains arabinoxylans, which may, under certain extraction conditions, contain a small proportion of ferulic acid side chains, which are readily cross-linked by enzymic oxidation. The cereal fibre fraction consists of the insoluble cellulosic residue remaining after the extraction of the arabinoxylan, and the removal of lignin and other impurities. The materials will be used as fat replacers and sources of dietary fibre.
- **3.** These materials, which are covered by Article 1(2)f of Regulation 258/97, are considered by the company to fall into category 2.1 of the European Commission's Guidelines on the Assessment of Novel Foods (foods and food ingredients isolated from plants, the source material for which has a history of use for food in the EU).

Alternatively, they could be considered to fall into category 6 (foods produced using a novel process). For either categorisation, the information requirements defined in these Guidelines are similar and the Committee's consideration of the data provided is presented according to these requirements.

I. SPECIFICATION OF THE NOVEL FOOD

(*The information on this aspect is provided in section 4.1 of the company dossier, and in Appendix 1 and 4*)

- 4. The specifications provided by the company require that the arabinoxylan fraction contains 85–91% carbohydrate, of which 24–34% is arabinose, 32–42% is xylose and 6–12% is galactose. The ferulic acid level of the ferulated arabinoxylan is between 0.25 and 0.5%. The protein content of the material is 4–8% and there are limits for heavy metals and for the ethanol and methanol used in the extraction process. The specification also contains microbiological standards for total viable count, yeasts and moulds and requires the absence of pathogens. The specification for the cereal fibre fraction requires it to contain a minimum of 90% carbohydrate (cellulose and hemicellulose) and contains similar microbiological standards as for the arabinoxylan fraction.
- 5. The company has provided analytical data on batches of the cereal fractions to show compliance with the specifications in terms of composition. These data are based on analysis of batches produced on a pilot plant scale and are fully compatible with detailed results obtained on a laboratory scale, used to define process control parameters to achieve a consistent quality. Any further upscaling of production is not expected to have any effect on the product specification. The process uses a heating stage (to 80° C) and alcohol precipitation, which reduces the microbiological load in comparison with the cereal bran starting material. Analyses of two batches of arabinoxylan ferulate powder (references 97/10/005, Lab Ref 186593 CIC/0056 and 97/11/007, LabRef 186594 CIC/0056) showed that they met the microbiological standards set in the specification. Analyses of three batches (97/12/017 LabRef 19321, 97/11/011 LabRef 19322 and 97/11/007 LabRef 19323) demonstrated that the limits for ethanol and methanol in the specifications were met. Polysaccharide chains may be degraded by high alkali concentrations; however data were provided from high performance liquid chromatography analyses to demonstrate that the molecular weight of the material remains essentially unchanged as the pH increases.

Discussion

Specifications have been provided the company (see Annex A attached to this report) and the opinion on these cereal fractions is conditional on the materials complying with such specifications. There are analytical data from batches of the soluble and insoluble fractions to show the range of composition and to demonstrate that they comply with the proposed specifications

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

(*The information on this aspect is provided in section 4.2 of the company dossier, and in Appendix 2, 3, 4, 10 and 11.*)

6. The process comprises aqueous alkali extraction of the cereal bran followed by precipitation with alcohol to obtain the arabinoxylan fraction. The extracted bran is then subject to aqueous alkali bleaching and separation to remove unwanted components, such as lignin, to produce the insoluble cereal fibre fraction. The chemical nature of the individual isolated fractions is, however, not significantly changed from that in the original cereal bran starting material in terms of their molecular weight profile. Aspects of the process are currently used in the manufacture of a number of existing food ingredients, such as aqueous extraction of citrus pulp and various seaweed species to produce pectins, carageenan and hydrocolloids. Appropriate factors to control the production process have been identified to ensure that the materials are produced consistently and to meet the

agreed specifications. Control of pH, temperature and time of extraction and other conditions are set in the process specification; deviation from the defined conditions influences the level of ferulic acid residues in the extracted arabinoxylan fraction. Data are provided on yield and ferulic acid content (as determined by UV absorbance) as functions of alkali concentration, pH and temperature for two batches of ferulated arabinoxylan. A HACCP study has been undertaken to determine the critical control points in the process (these are control of pH, temperature and time of extraction) to ensure compliance with the specifications and that no toxicological, nutritional or microbiological hazards arise.

Discussion

The process as a whole has not previously been used in the production of food ingredients but various elements are used in the production of existing food ingredients such as pectins and carageenans. The process is well characterised and the critical control points (control of pH, temperature and time of extraction) have been identified to ensure that consistent products are obtained that do not represent any toxicological, nutritional or microbiological hazards.

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

(The information on this aspect is provided in section 4.3 of the company dossier.)

7. The novel foods could be derived from any cereal brans, however this application is restricted to using bran from maize (Zea mays) and wheat (Triticum aestivum and related species), both of which are staple foodstuffs. The company has stated that it does not intend to use material from genetically modified cultivars at this time; however, such cultivars might be used in future if they were in common commercial use. The extraction process used would denature any genetic material present in the starting cereal bran material.

Discussion

The cereal bran starting materials used to produce these fractions are obtained from conventional maize and wheat cultivars.

IV. ANTICIPATED INTAKE/EXTENT OF USE OF THE NOVEL FOOD INGREDIENTS

(The information on this aspect is provided in section 4.4 of the company dossier.)

- 8. Both cereal fractions will have two main uses, as fat replacers and as sources of fermentable carbohydrate. The arabinoxylan fraction would be used as an aqueous solution to replace fat, to provide body, viscosity, appearance and mouthfeel. The likely range of uses would include dairy desserts, yoghurts and ice cream (at levels of 1–2%), salad dressings (at 2–3%), comminuted meat products such as sausages and burgers and their vegetarian equivalents (at 1–2%) and low- and reduced-fat spreads (at levels up to 2%). The cereal fibre is also likely to be used in these products, but it also expected to be used in baked goods, batters and crumb coatings and creme fillings at levels up to 5%. In some applications, it may be used as a dry component but in other applications, where maximum water binding is required, it is likely to be used as a sheared dispersion in water. Food manufacturing companies may in time develop other products containing these cereal fractions but these would be expected to be "reduced fat/high fibre" products rather than mainstream food products.
- **9.** The use of the cereal fractions is not likely to be restricted to particular population groups and the company has provided estimates of possible intakes, making assumptions about

the consumption of a number of food products that may contain the fractions. Thus, if 3 products were consumed in one day (for example yoghurt, ice cream and sausages), the maximum intake of the arabinoxylan fraction would be 6g/day. However it is likely that the intake would be less than this on a regular basis, with an average likely intake of up to 2g in a single day. Similarly, a possible intake for the cereal fibre fraction was calculated assuming consumption of 4 items (dairy dessert, bread, cake with creme filling and breaded fish) giving an intake of 15g/day; again, the intake is likely to be less than this on a regular basis.

10. The introduction of these cereal fractions is not likely to be limited on a geographical basis. The fractions are likely to replace some of the fat in the products in which they are used. This switch from fat to fermentable carbohydrate is in line with recommendations from a number of government health authorities and is expected to have a beneficial effect on health in most population groups. It is possible that this might have an adverse consequence in young children, in whom the immature gut may ferment such materials very rapidly, leading to diarrhoea. This issue is addressed under section VI, relating to nutrition.

Discussion

Intakes have been calculated on the basis of consumption of a number of food items in which the cereal fractions are expected to be used, giving maximum figures of 6g/day of the arabinoxylan fraction and 15g/day of the cereal fibre; however, it is unlikely that all these products will be consumed each day on a regular basis and thus the average daily intake is likely to be lower.

The nutritional consequences of the use of these materials is addressed more fully in section VI, nutrition.

V. INFORMATION ON PREVIOUS HUMAN EXPOSURE

(*The information on this aspect is provided in section 4.5 of the company dossier, and in Appendix 5.*)

- 11. The fractions are obtained from maize and wheat bran, which are part of the normal diet in Western Europe. Consumption of unrefined cereals had been declining in modern times but recently the intake of cereal brans has been increasing again in certain sections of the population. The company has noted that other cereal fibre products are already on the market, and that in addition, one other arabinoxylan extract is also available, although the pH at which this is extracted is not known.
- 12. The company notes that cereals, especially wheat, can give rise to food intolerance in susceptible individuals, but such reactions are only mild with maize. This is a generic problem and is linked to the gluten proteins present in the cereal. The extraction process used to obtain these fractions is designed to remove such gluten proteins but small amounts may remain. The company intends to address this issue by clear labelling of the presence of the cereal fractions in the final food products so that those intolerant to wheat may avoid such foods. The labelling proposed is "soluble wheat extract/wheat extract" or "wheat fibre".

Discussion

There is a considerable history of consumption of unrefined cereals and cereal brans in Europe. Certain individuals may be intolerant to wheat gluten proteins but it is intended that the foods containing these ingredients will be fully labelled so that such people may avoid them.

VI. NUTRITIONAL INFORMATION

(*The information on this aspect is provided in section 4.6 of the company dossier, and in Appendix 6, 7 and 8.*)

- **13.** The use of either of the cereal fractions will result in the replacement of some fat in the diet by fermentable fibre, a switch that is recommended by many government health authorities. The company has considered the possible effect of the phytate in the cereal on the bioavailability of minerals, such as calcium and iron, in the diet. The extraction process used to obtain the cereal fractions reduces the level of phytic acid compared with that found in the cereal bran starting materials. The maximum phytate level is seen in the arabinoxylan ferulate extract (1.2%) whereas that in wheat bran is 6% and that of wholemeal flour is 1.5%. This fact, together with the envisaged usage levels of the cereal fractions, suggest that it is unlikely that the incorporation of these ingredients in foods will have any significant adverse effects on mineral bioavailability.
- 14. Fermentable carbohydrate passes into the large intestine essentially undigested, where it is fermented by the gut bacteria, producing short chain fatty acids (SCFAs) such as acetate, butyrate and propionate, and dicarboxylic acids such as lactate and succinate and gases, mainly hydrogen. SCFAs are considered to be positive contributors to gut health. The rate of fermentation of a given diet varies between people and is dependent on the make up of the gut flora. Young children are particularly susceptible to the effects of rapid fermentation, resulting in diarrhoea.
- 15. Cellulose, like other insoluble glucose polymers, is only fermented to a relatively low degree. The fermentability of cellulose has been compared (Barry, Hoebler et al 1993) with other materials (maize bran, soya bean fibre, sugar beet fibre and pectin) demonstrating the low fermentability of cellulose and maize bran. However, no actual experimental data have been provided for the insoluble cereal fraction described in this application. Similarly, although no specific studies were conducted on the arabinoxylan extract described in this application, reference to the literature (Englyst, Hay and MacFarlane, 1987) demonstrates that purified pentosans (arabinogalactan and xylan) are broken down relatively slowly compared with starch (48 hours and 6 hours respectively for a reduction in the arabinoxylan concentration from 9 to 2 mg/ml) and that pectin is broken down relatively rapidly. A further reference (Stevens, Selvendran et al 1988) confirms the low rate of fermentation of non-starch polysaccharide from wheat bran compared with that of pectins from apple cell walls. Starch that escapes digestion (approximately 10% of that ingested – a range of 8-40g/day) is rapidly and completely fermented in the large bowel (MacFarlane and Englyst 1986, and Cummings and MacFarlane 1991). The company has stated that the SCFAs produced from fermentation of their materials will be insignificant in comparison with that produced from the starch present in most meals.
- 16. The company commissioned one study to support their general conclusions, based on the scientific literature. In this in vitro study, (Appendix 7 of the company dossier) the rate of fermentation of arabinoxylan, arabinoxylan ferulate and starch by inocula of faecal bacteria from children (aged from 2–5years old) was investigated, in terms of the rate of substrate digestion and the types, amounts and rates of fermentation product formation. Fresh faecal samples were obtained from eight children. Production of SCFAs and other organic acids was monitored over 48 hours, as was residual carbohydrate. Intestinal micro-organisms were isolated and characterised. Although there was considerable variation between samples, starch was consistently degraded more rapidly than either of the arabinoxylans. Arabinoxylan ferulate was degraded more slowly than the non-ferulate fraction.

Arabinoxylan and arabinoxylan ferulate were metabolised to SCFAs (acetate and propionate) but no lactate formation was detected, although low levels of succinate were found. Starch, on the other hand, was consistently metabolised to produce high, but transient levels of lactate, and butyrate was the main SCFA produced. Fermentation of the arabinoxylans did not result in any major shifts in microbiological composition. It was concluded that these materials behave in a similar way to other fermentable non-starch polysaccharides in the way that they are fermented. The company has indicated that it intends to publish this study in the scientific press.

17. An adult 7-day feeding study was also conducted (Appendix 8 of the company dossier) using a double blind crossover design with a 7-day washout period. Volunteers consumed either test foods providing a minimum of 10g per day of the trial material or control foods without added fermentable carbohydrate. Food intakes, subjective measures of gut function, satiety and mood were monitored. No significant differences were noted after consuming the test and control foods in any of the factors assessed.

Discussion

The company has used the existing scientific literature to support the view that the use of these materials in foods would have a positive nutritional outcome as a result of replacing some fat with fermentable carbohydrate. There is literature evidence to support the view that these materials are fermented relatively slowly, compared with materials such as starch and pectins. Therefore, as a result, there would only be a gradual production of SCFAs, and thus no adverse consequences from their incorporation into foods at the levels proposed. An adult 7-day feeding study and a study using inocula from faecal samples from young children has confirmed that negative nutritional effects are unlikely to occur, even in the immature gut.

VII. MICROBIOLOGICAL INFORMATION

(*The information on this aspect is provided in section 4.7 of the company dossier, and in Appendix 9.*)

18. The cereal fractions are obtained from food grade cereal bran and the HACCP system for the process contains a number of microbiological control points for the starting materials and their introduction into the process. The extraction process itself has a number of steps that are likely to reduce the microbiological load and other critical control points in the extraction and drying steps have been identified. In addition the specification for the final food ingredients contains microbiological limits that are lower than for many cereal products. The analyses of two batches of arabinoxylan ferulate powder reported in Appendix 9 show that the levels found were well within the specification limits. The company has included additional precautions to prevent adventitious microbial contamination of the product prior to dispatch to food manufacturers.

Discussion

The microbiological loading of these materials is likely to be less than that of the cereal bran from which they are obtained and is controlled during the extraction process. The specifications for the final materials contain microbiological limits, and steps have been introduced to prevent adventitious microbial contamination prior to dispatch to food manufacturers.

VIII. TOXICOLOGICAL INFORMATION

(*The information on this aspect is provided in section 4.8 of the company dossier, and in Appendix 10 and 11.*)

- **19.** There are no natural toxicants present in the cereal bran starting materials. The extraction process does not introduce any toxicants and the levels of the methanol used to precipitate the arabinoxylan are controlled by the specification of the final material. Analyses are provided to demonstrate compliance with such specification limits.
- **20.** Evidence obtained from HPLC studies using 2 concentrations of alkali (0.5% and 5%) demonstrates that there is no significant degradation to lower molecular weight species during the extraction process.
- **21.** The possible intolerance risk of the materials is discussed in paragraph 12 but is likely to present a lesser hazard than the cereal bran starting materials. In addition the company intends that foods containing cereal fractions obtained from wheat should be fully labelled.

Discussion

Neither the cereal bran starting materials nor the extraction process are likely to give rise to any toxicants in the final product. Evidence is presented to show that the alkali extraction process does not result in material with a higher proportion of lower weight molecular species.

Overall discussion

22. Information has been provided on all the areas appropriate to a novel food falling in category 2.1 of the EC Guidelines. There is a specification for the final food ingredients and the process by which they are produced is well defined and controlled. A description is given of the types of food product that these materials are expected to be used in and the likely levels of incorporation. Estimates of intake of these cereal fractions by people consuming a number of such food products have been provided. Information on the nutritional consequences of using these ingredients in food to partially replace fat or as fibre sources has also been provided and there is evidence to support their safety for such uses. In particular, information is provided to show that these ingredients would be fermented relatively slowly in the large bowel, in comparison with starch and pectins. Therefore, their consumption would not lead to adverse gastrointestinal consequences arising from the rapid release of short chain fatty acids, even in the immature gut of children.

Conclusions

23. Du Pont (UK) Ltd has made an application to the ACNFP for approval to market two cereal fractions obtained from wheat or maize bran. Based on the advice of the ACNFP, the UK competent authority has concluded that the evidence provided supports the view that the fractions obtained by the alkali extraction of cereal brans are safe for use in food in the applications described, provided that they met the specifications set out and attached to this report.

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Appendix III

UK Competent Authority initial assessment report on the safety of Salatrims – a family of reduced calorie fat replacers

Applicant:	Danisco-Cultor, formerly Cultor Food Science (Xyrofin UK Limited)
Responsible person:	Mr N Baldwin
Novel Food:	Salatrims, a family of low calorie fats for use in bakery and confectionery food products.
EC Classification	2.1

Introduction

- 1. The UK Competent Authority accepted an application from Cultor Food Science1 for clearance of Salatrims, a family of low calorie fat replacers, under the EU Novel Food Regulation on 28 June 1999. The UK had previously considered data on Salatrims under the voluntary scheme for novel foods that existed in the UK prior to the introduction of the EU Regulation in May 1997. A number of concerns had been identified in the original consideration of these materials and these concerns have been addressed in the current application. During the consideration of the data, the Advisory Committee on Novel Foods and Processes (the UK assessment body) sought clarification of a number of issues and supplementary papers to answer these points were submitted by the company on 24 and 27 August 1999^{2,3}.
- 2. Salatrims (Short And Long chain Acyl TRIglyceride Molecules) are a family of structured triglycerides composed predominantly of mixtures of long chain fatty acids (principally stearic) and short chain organic acids (acetic, and/or propionic and/or butyric) esterified with glycerol. They are prepared by the interesterification of glycerol esters using a process routinely used by the edible oil industry. The materials are designed to provide fewer calories than conventional fats, but to have similar technological properties. This application is restricted to the use of Salatrims in bakery and confectionery food products.
- 3. Much of the information summarised in the application has been published in the Journal of Agricultural and Food Chemistry⁴, and is also contained in the GRAS affirmation petition submitted to the UD Food and Drug Administration⁵, and in the report of an expert panel of the Life Sciences Research Office of the Federation of American Societies for Experimental Biology⁶. Salatrims have also been evaluated by the FAO/WHO Joint Expert Committee on Food Additives⁷.
- 4. According to the EC guidance on the classification of novel foods, Salatrims are classified as Class 2.1 complex novel food from non-GM sources, where the source of the novel food has a history of use in the Community. The information provided on Salatrims is addressed below, according to the requirements for this class of novel food. The location of the information in the summary document and the full application dossier are given for each of the information areas detailed below.

I. SPECIFICATION OF THE NOVEL FOOD

(Information on this aspect is provided on page 2 of the summary document and in Appendix 1a of the company dossier)

- 5. A proposed generic specification has been provided by the company, which is attached to this opinion (Annex I). The fatty acid composition of Salatrims can be varied to give differing technological properties and certificates of analysis for five Salatrim variants are included in the application.
- 6. The proposed specification states that Salatrims contain >87% triacylglycerols. The fatty acid composition can be varied to confer differing technological properties. The proportion of short chain organic acids (acetic, propionic and butyric acids) can vary between 33 and 70% and that of long chain fatty acids (mainly stearic acid) varies between 30 and 67%. The fatty acids used in the manufacture of Salatrims can be sourced from a number of hydrogenated oils (canola, soya bean, and cottonseed). These oils may be derived from approved genetically modified plant varieties, where such oils meet the normal specifications for edible oils. Further details of the composition of the Salatrims used in the safety studies supporting this application are given in the first statement from the Committee on Toxicity (Annex II to this opinion).

Discussion

We accept the principle of setting a generic specification to cover the family of Salatrims, with certificates of analysis to define the composition of individual Salatrim variants, as described in the company documentation.

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

(Information on this aspect is provided on page 3 of the summary document and in Annex 1b, paper 6 of the company dossier)

7. The production process used to manufacture Salatrims is commonly used in the edible oils and fats industry to modify the physical properties of edible oils, and the raw materials used are of food grade quality. The process consists of the interesterification of long chain saturated fatty acids (derived from hydrogenated soya, canola and cottonseed oils) with an excess of triacetin and/or tripropionin and/or tributyrin, using a sodium methoxide catalyst. The catalyst is deactivated with distilled water when the reaction is complete and the oil is then washed, bleached and filtered. Any residual mono- and diglycerides are converted to the corresponding triglycerides, as necessary, and any residual short chain triglyceride is reduced to less than 1% by vacuum and steam stripping followed by vacuum distillation. The composition of the particular Salatrim variant is determined by the molar ratios of the starting materials used (1.5–12 molar excess of the short chain fatty acids) and actual composition is highly correlated to that predicted (see published paper in Journal of Agricultural and Food Chemistry⁴).

Discussion

The production process used to produce Salatrims is not novel and the actual composition of the materials produced reflects that predicted from the proportions of the starting materials used.

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

(Information on this aspect is provided on page 3 of the summary document.)

8. Salatrims are derived from hydrogenated soya, canola and cottonseed oils, all of which has a long history of safe use within the European Community, as sources of edible oils. The oils may be derived from genetically modified varieties that have obtained approval as novel foods, where the composition of such oils meets the normal requirements for edible oils.

The source organisms from which the oils from which Salatrims are produced have a history of safe use in the production of edible oils in the European Community.

IV. ANTICIPATED INTAKE /EXTENT OF USE OF THE NOVEL FOOD

(Information on this aspect is provided on pages 3 and 4 of the summary document and Annex 1a, paper 2, of the company dossier.)

- 9. This application is limited to seeking approval for use of Salatrims in bakery and confectionery food products only. The company has stated that Salatrims are not intended for use in infant formulas and their technical properties preclude their use as frying oils/fats. They are intended for sale to the food processing industry for use in manufactured products and will not be available directly to the consumer. The range of uses permitted in the USA is wider than that applied for in the Community.
- 10. The main food products in which it is envisaged that Salatrims will be used are chocolate, chocolate confectionery, other chocolate products, buns and pastries, and cookies and brownies. The company has used data from the UK National Dietary and Nutrition Surveys for adults' food consumption, together with information on the fat content of foods, to estimate a mean intake of Salatrims of 11g/day, with a 97.5th percentile intake of 33g/day. Products containing Salatrims will be aimed at those people choosing a restricted calorie diet. The Company has suggested that such products are likely to carry a price premium and will not be aimed at young children. For this reason, intake estimates have not been generated for young children.

Discussion

The company has applied for a limited range of uses for Salatrims in the first instance of bakery and confectionery food products only. Data from UK surveys have been used to estimate mean and extreme intakes of Salatrims in adults, assuming replacement of all possible fat in the specified target food products by Salatrims. Such estimates are therefore likely to be overestimates, even in those consumers who actively seek Salatrim food products. No estimates for intakes of Salatrims by children have been provided. As a general principle, young children do not need to restrict their energy intake and therefore, on nutritional grounds, foods containing Salatrims should not be aimed at this age group Data from a recent UK National Diet and Nutrition Study (in press) has shown that older children and adolescents (11–18 year olds) eat approximately the same quantities as adults of most of the food categories that Salatrims might be used in (biscuits, and buns, cakes and pastries), although their consumption of confectionery was somewhat higher. From this it can be inferred that the estimates of absolute amounts (grams per day) of Salatrim that might be consumed by adults would also be appropriate for older children and adolescents. The company has indicated that a further application would be made to seek approval for any extension in the range of food categories in which Salatrim could be used.

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

(Information on this aspect is provided on pages 4-6 of the summary document.)

- 11. Salatrim structured triglycerides contain at least one short chain organic acid (acetic and/or propionic and/or butyric) and at least one long chain saturated fatty acid (primarily stearic). These fatty acids and glycerol are common components of the normal diet or are formed by colonic bacteria and the levels of intake anticipated from consumption of Salatrim food products are not associated with any adverse health effects (see also section VIII on toxicological information).
- 12. Data on the composition of Salatrim fats have not shown the formation of any unexpected by-products of the production process, nor has the presence of any unexpected, non-acylglycerol components been demonstrated. Levels of phytosterols, tocopherols, unsaponifiable components and organic constituents are found at levels comparable to, or lower than, those found in conventional oils and fats. Pesticide residue levels in Salatrim fats are comparable to the levels found in the commercial hydrogenated fats from which they are derived.
- 13. Post-market data from self-reporting systems in the USA (toll-free telephone calls, internet and mail), where Salatrim food products have been on the market since 1995, indicate only a low incidence of possible gastrointestinal tract effects following consumption.

Discussion

The constituents of Salatrims are common components of the normal human diet and the levels of intake arising from the consumption of Salatrim food products are not associated with any known adverse health effects. The results of toxicological studies in animals and of human volunteer studies are addressed later in this document.

VI. NUTRITIONAL INFORMATION ON THE NOVEL FOOD

(Information on this aspect is provided on pages 7-10 of the summary document and Annexes 1a (papers 3, 4, 5, 9 and 10), 1b (papers 2, 10 and 15-21), 3 and 5a of the company dossier)

- 14. The use of Salatrim in food products in place of conventional fats can result in an increase in the dietary intake of saturated fats. However, the total dietary intake of calories from fat will decrease. This is because although the absolute intake of stearic acid is increased following substitution of conventional fats by Salatrim, not all of this stearic acid is absorbed.
- 15. In addition, the use of Salatrim will displace from the diet other saturated fats, such as palmitic, myristic and lauric acids, whose consumption is known to be associated with increases in serum cholesterol levels. The company has reviewed the literature on the cholesterolaemic effect of stearic acid and has suggested that it is neutral in this respect in relation to fatty acids such as lauric and myristic. The company also noted that stearic acid does not induce changes in platelet phospholipids, nor does it increase the tendency for thrombosis.
- 16. The ACNFP, in its initial consideration of the safety of Salatrims, had identified thrombogenic potential as a possible area of concern. In response to this concern, the company has conducted studies in humans to address this issue and the results are included in the current application. A single dose study was conducted in volunteers, who

were at moderately increased risk of coronary heart disease, to investigate post-prandial changes in various markers of fibrinolytic activity. Subjects were middle-aged and had moderately raised plasma cholesterol levels (between 5.2 and 7.8mmol) and were also moderately overweight. These subjects consumed test meals rich in Salatrim or one of two control meals (containing equivalent amounts of oleate-rich sunflower oil or cocoa butter). The post-prandial increase in serum triglycerides seen after consumption of the Salatrim meal was lower than those seen after the control meals. Fibrinolytic activity (as measured by tissue plasminogen activator activity and plasminogen activator type I activity) was not affected by the different fats present in the test meals. However, plasma factor VII coagulant activity and the plasma concentration of activated factor VII were increased to a lesser extent after the Salatrim meal in relation to the two control meals. The company also conducted a five-week crossover study in hypercholesterolaemic subjects on margarine's enriched with Salatrim or palm oil. This study showed no evidence of any increases in factor VII coagulant activity or fibrinogen following consumption of Salatrim.

- 17. The company has considered whether consumption of Salatrims could impair the absorption of fat-soluble vitamins. The results from a number of studies in both animals and human volunteers support the view that Salatrim does not affect the absorption of vitamins A and E. In addition, the physico-chemical properties of Salatrim would not suggest that it would have an adverse consequence on fat-soluble vitamins.
- 18. The Salatrim family of structured triglycerides has been designed to provide 4–6 calories/g rather than the 9 calories/g supplied by traditional fats. This reduced caloric value is partially attributable to the presence of the short chain organic acid constituents, which are less energy dense than long chain fatty acids, and partially to the incomplete absorption of the stearic acid component, which is the predominant long chain fatty acid constituent. The company has provided evidence from a two-week growth assay in rats to support a reduced caloric intake from Salatrim, in relation to conventional fats. The company is claiming that this study, and other supporting data, would suggest a caloric value of Salatrim of the order of 5–6 calories/g.

Discussion

The experimental data supplied do not provide any evidence to suggest that Salatrims have any acute adverse effects in the post prandial period with respect to the enhancement of thrombogenesis or the impairment of fibrinolysis, in healthy subjects at moderately increased risk of coronary heart disease. It is noted that the half-life of factor VII is relatively short and thus it would appear unlikely that the effects of chronic consumption of Salatrim would be different to the effects of acute consumption. Repeated dose studies in hypercholesterolaemic subjects did not show any evidence of adverse effects on factor VII coagulant activity, fibrinolytic activity and platelet or endothelial function following consumption of 30g/day Salatrim for five weeks.

It is concluded that there is evidence that consumption of Salatrim would not have any adverse effects on thrombogenic potential, even in those at moderately increased risk of coronary heart disease.

Consideration of the physico-chemical properties of Salatrims and the partitioning theory of fatsoluble vitamin absorption would suggest that consumption of Salatrim would not impair the absorption of fat-soluble vitamins. In addition data from animal studies with Salatrims have shown no evidence of adverse effects on fat-soluble vitamin absorption.

It is accepted that Salatrims are likely to supply significantly fewer calories per g than conventional fats. However we are not in a position to determine a suitable figure for the caloric value of Salatrims

for food labelling purposes. In order that the consumer is not misled, there is a requirement under the Novel Food Regulation for foods containing Salatrims to be labelled with information on their true caloric value. However, current European Commission nutrition labelling rules require that all fats are labelled to indicate that they supply 9calories/g. This conflict needs to be resolved within the European Commission. We note that products containing Salatrims that are marketed in the USA are labelled to inform the consumer of the reduced caloric value of the Salatrim ingredient.

VII. MICROBIOLOGICAL INFORMATION ON THE NOVEL FOOD

(Information on this aspect is provided on page 10 of the summary document.)

19. Salatrims are manufactured under the normal Good Manufacturing Practices guidelines and the oil phase precludes the growth of typical food borne micro-organisms.

VIII. TOXICOLOGICAL INFORMATION ON THE NOVEL FOOD

(Information on this aspect is provided on pages 10–20 of the summary document and in Annexes 1a (papers 4, 7, 8, 11, 12 and 13), 1b(papers 12–21) and Annex 4 of the company dossier and in the additional information supplied on 24 August 19992).

20. A number of animal toxicology and human clinical have been conducted to investigate the safety of Salatrims. The studies have tested a number of representative Salatrim variants, covering the range of commercial products. The ACNFP sought the specialist advice of it's sister committee, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) on the testing strategy adopted for Salatrims and on the results obtained. The COT first considered Salatrims in 1997, before the Novel Food Regulation came into effect, and issued a statement summarising the toxicological and clinical data then available. The COT identified a number of concerns at that time, which have been addressed in the application made under the Regulation. The new data and arguments have also been considered by the COT and that committee has now issued a further statement of it's views. These statements are attached as Annexes II and III to this opinion.

Discussion

We fully endorse the views of the Committee on Toxicity, as set out in their statements attached to this opinion. In particular, we accept that although there were increases seen in serum hepatic enzyme activities in some individuals, statistically the activities were still within the normal range(s) of variation. In addition we note that increases in hepatic enzyme activities of a similar magnitude were also seen in some individuals receiving the control fat. In the absence of any other indicators of liver damage we consider that these changes in hepatic enzyme activities do not represent a clear toxic effect.

We also accept that the gastro-intestinal symptoms reported are likely to arise from individual intolerances to large amounts of Salatrims, rather than from any toxic effect. In our opinion, these effects would be likely to limit the consumption of Salatrim products in such susceptible individuals and therefore such effects do not represent a safety concern. We also note that there is variation in the tolerance of individuals to conventional fats.

Overall discussion

21. Salatrims are a series of structured triglycerides that have been designed to provide fewer calories than conventional fats. They are manufactured from traditional food sources using existing food processing technologies. The company has sought clearance for the use of

Salatrims in a restricted range of food products, namely baked goods and confectionery, and has estimated average and extreme intakes of Salatrims in adults arising from such uses, assuming maximum substitution of conventional fats in these products by Salatrims.

- 22. The company has provided data from a range of animal and human studies to support the safety-in-use of Salatrims. They have addressed a number of concerns that had been identified in the course of the safety evaluation, namely possible thrombogenic effects, possible toxicity of the short chain organic acid component of Salatrims, possible hepatotoxicity and gastro-intestinal tract symptoms.
- 23. On the basis of the totality of the data now provided to us, we are satisfied that Salatrims are acceptable for use in the food product categories described in the application, namely baked goods and confectionery. Any extension of the range of use of Salatrims to other food categories would require a further approval. We note that there are no specific safety data relating to possible effects of Salatrims in children. However, data from a recently completed, but as yet unpublished, diet and nutrition study in the UK, has indicated that older children consume approximately equivalent amounts of the food products that Salatrims would be used in as adults, with the exception of confectionery, where intake is somewhat higher than in adults. As a general principle, young children do not need to restrict their energy intake and therefore, on nutritional grounds, foods containing Salatrims should not be aimed at this age group. However, the question of the applicability of any low calorie/low fat food products for this young age group is a generic one, that is not restricted just to consideration of foods containing Salatrims.
- 24. We accept that Salatrims provide fewer calories than conventional fats and we recommend that the consumer should be provided, via labelling on the products themselves, with information on the true caloric value of foods containing Salatrims. This is in conflict with the provisions of the present Nutrition Labelling Directive and this issue will need to be resolved at European Commission level.

Conclusions

- 25. We have considered the information presented in the application dossier and the supplementary information provided in response to specific questions raised during our evaluation and we conclude that Salatrims, as specified, are acceptable for use in the food products described, that is in baked goods and confectionery. A further application would need to be made before the use of Salatrims could be extended to other food products.
- 26. We accept that Salatrims supply fewer calories than conventional fats. We recommend that consumers should be supplied with appropriate information on this aspect, and that this may require amendment of the provisions of the Nutrition Labelling Directive.

References

- 1. Submission for approval under Regulation (EC) No 258/97 of the European Parliament and the Council of 27th January 1997 concerning novel foods and novel food ingredients, for the use in bakery and confectionery food products of the family of low calorie fats known as "SALATRIMS". *Cultor Food Science (Xyrofin UK Limited)*. 26th May 1999.
- 2. Supplementary information on serum hepatic enzymes and dropouts from the free-living clinical study. *Cultor Food* Science. 24th August 1999.

- 3. Supplementary information on thrombogenic potential. *Cultor Food Science*. 27th August 1999.
- 4. Journal of Agricultural and Food Science, 42, 2, pages 432–604. 1994.
- 5. US GRAS affirmation petition. 1994.
- 6. The evaluation of the health aspects of using certain triacylglycerols as food ingredients. *Life Sciences Research Office of the Federation of American Societies for Experimental Biology*. 1993.
- World Health Organisation, 1998. Salatrim (short and long chain acyltriglyceride molecules). In: Safety Evaluation of Certain Food Additives and Contaminants. WHO Food Additive Series, No 40, pages 111–141. Geneva: WHO.
- 8. National Diet and Nutrition Survey for young people: 4–18 years. 1999. *In Press*.

Annex I to Appendix III

Proposed specification for salatrims

Description	Clear, slightly amber liquid to a light-coloured waxy solid at room temperature. Free of particulate matter and of foreign or rancid odour
Glycerol ester distribution	
Triacylglycerols	>87%
Diacylglycerols	<10%
Monoacylglycerols	<2%
Fatty acid composition	
Mole % LCFA (Fatty acid profile)	33-70%
Mole % SHOA	30-67%
Trans fatty acid	<1%
Free fatty acids as oleic	<0.5%
Triacylglycerol ACN Profile	
Triesters (s/l of 0.5 to 2.0)	>90%
Triesters $(s/l = 0)$	<10%
Unsaponifiable material	<1%
Moisture	<1%
Residue on ignition	<0.1%
Heavy metals (as Pb)	<10ppm
Lead	<0.1ppm
Arsenic	<0.5ppm
Colour	<3.5 Red (Lovibond)
Peroxide value	<2.0 Meq/Kg

Annex II to Appendix III



Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Statement for the Advisory Committee on Novel Foods and Processes on short and long chain triacyl glycerol molecules (Salatrims) – a family of low calorie fats

Introduction

- 1. We have been asked by the Advisory Committee on Novel Foods and Processes (ACNFP) to comment on specific aspects of a large submission of data received by the ACNFP in respect of Salatrims, a family of low calorie fat products. The ACNFP reviewed the available toxicological and clinical safety data on Salatrim at its 32nd meeting on 26 September 1996. The ACNFP requested advice from the Committee (COT) in respect of:
 - the adequacy of the animal toxicological database and, in particular, the arguments proposed by Cultor Food Science, who wish to market these products in the UK, regarding limited testing of Salatrims in animals.
 - an evaluation of the increases in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) documented in human clinical studies and, for comments regarding the lack of predictivity of the animal toxicology studies in respect of these effects on the liver.
- 2. Salatrims comprise a family of structured glycerides composed predominantly of mixtures of long chain fatty acids (LCFAs; principally stearic acid) and short chain fatty acids (SCFAs; acetic, propionic and/or butyric) which are intended as low calorie fats for use in soft sweets, coatings (e.g. wafers and confections), dairy products, shortening and potentially in table spreads. Predicted intakes will vary according to the uses of Salatrims, level of substitution for existing fats, and the extent to which these fatty acids are consumed. We have considered several reports provided by Cultor Food Science, which present calculations regarding potential intakes. The estimated intake for the whole population assuming selected uses varied between 11–29 g/day (mean), and 18–65 g/day (97.5th percentile).

Estimates of intake using all potential uses varied between 18–46 g/day (mean) and 30-88 g/day (97.5th percentile). We also note that the Joint Food and Agriculture Organisation/World Health Organisation Expert Committee on Food Additives estimated intakes in children aged 3–5 years to be approximately 26 g/day (90th percentile). We *note* that there are considerable uncertainties regarding the methods and precision of the calculated estimates of potential Salatrim intake and that the various figures provided by the company show a wide variation. We are also *aware* that children have a caloric intake, which on a body weight basis is higher than that in adults, on which basis their exposure to Salatrim would also be higher. Thus it would have facilitated interpretation of the intake data if the latter had been calculated and expressed in terms of grams Salatrim/kg bw/day and grams Salatrim/energy intake/day. However, we *consider* that the available figures provided by the company can be used as a guide to the evaluation of the clinical and toxicological data provided in the submission.

- 3. An abbreviated nomenclature has been used by the manufacturers and also throughout this statement to describe the various Salatrims which have been evaluated in toxicological and clinical safety studies. An account of this nomenclature and details regarding all Salatrims tested are given in tables 1 and 2 of the Annex to this statement. (For example, in Salatrim 43SO tributyrin and tripropionin are the SCFAs and the LCFA source is hydrogenated Soybean Oil.)
- 4. The specific questions raised by the ACNFP with regard to Salatrims were considered by the COT during 1996 and at a joint ACNFP/COT Working Group in early 1997 where representations from the company were heard. Following this latter meeting, additional information regarding intakes and evaluation of the animal toxicity and human clinical studies was submitted to the COT. A short summary of the available animal and human toxicology data on Salatrims is given below for information so that our consideration of the questions raised by the ACNFP can be placed into context.

Animal metabolism/Toxicity data

- 5. Initial in-vitro studies of the hydrolysis of Salatrim products using porcine pancreatic lipase demonstrated that a wide range of Salatrim triacylglycerides underwent rapid hydrolysis. In-vivo metabolism experiments in rats were designed to compare the metabolism of a specified Salatrim (23CA) with triolein and the results showed that Salatrim 23CA was metabolised in an analogous way to triolein (a normal dietary fat).
- 6. Five 90-day feeding studies were undertaken in rats using a range of Salatrim products selected to include different combinations of short chain fatty acids (i.e. acetate, propionate, butyrate) and different sources of stearate (i.e. canola oil, cottonseed oil and soybean oil). Details regarding the Salatrim products tested are given in table 2 of Annex 1. The results of the toxicity studies were consistent, showing no toxicologically significant effects at up to 10% w/w in the diet (i.e. approximately 6-8 g fat/kg bw/day).

The observed changes in clinical chemistry and histopathological findings noted in these studies, which occurred predominantly at 10% w/w in the diet and consisted of alterations in bone mineral levels (e.g. increased bone zinc concentrations), and of renal mineralisation in female rats, were considered by the authors to be consistent with alterations in mineral metabolism induced by a reduced proportion of polyunsaturated fats in the diet. The authors of the animal toxicology studies noted that published evidence is available which reported diet induced alterations in mineral metabolism, and in particular reduced bone zinc concentrations in rats following administration of diets containing high levels of polyunsaturated fatty acids. (Lusak & Johnson, 1992) Dietary administration of 10% w/w Salatrim 23SO to rats for up to 17 days had no effect on serum activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT) or (glutamyltransferase (GGT) activities, although increases in the levels of serum enzyme have been documented in the human clinical studies. No toxicologically significant effects were documented in a 28day study in minipigs fed a diet containing 10% w/w Salatrim 23SO. Samples of caecum were taken during routine necropsies of the rats fed Salatrim 23CA or 32CA for 13 weeks, frozen and then subsequently analysed for gut microflora and for evidence of any Salatrim induced changes in caecal pH, and primary/secondary metabolites of bile acids and phytosterols and for cholesterol and coprostanol levels. There was no evidence of any effects on gut microflora from these experiments. We note that the morphological methods used in these investigations to assess effects on gut microflora were insensitive. Salatrim products do not contain any structural alerts for potential mutagenicity. There was no

evidence of genotoxicity in an adequate range of *in-vitro* or *in-vivo* studies. No studies to evaluate potential carcinogenicity or effects on reproduction are available.

Human toxicity data

- 7. Four clinic-based studies using adult volunteers have been undertaken which utilised double blind study designs. The experimental protocols used exposures up to 60 g Salatrim/day for 1, 4 or 7 days and study designs that included a 4-day triple crossover experiment. This type of design allowed the effects of three different fat sources on clinical chemistry and recording of symptomatology to be compared in the same individuals, but we *note* that only a very short exposure period of 4 days was used. The results of the clinic based studies with tested Salatrim products showed similar effects on gastrointestinal function (i.e. nausea, stomach cramps, diarrhoea, flatulence were reported) at 60 g/day. These effects subsided when the Salatrim administration was stopped. Overall, the authors concluded that 30 g Salatrim/day in the clinic-based studies did not result in any gastrointestinal effects. We *note*, however, the limited duration of these studies and that clinical investigations were only performed on healthy adults and thus potential effects in children or individuals with compromised gastrointestinal function were not considered.
- 8. A 28-day free living study was undertaken using groups of at least 12 male and 12 female volunteers consuming a range of food products containing one of three Salatrim products (23SO, 43SO, 4SO) at levels of up to 60 g Salatrim/day. The purpose of this study was to allow an extended evaluation of the Salatrim products and to confirm the effects seen in the clinic-based studies and also to determine if any of these effects were reversible. The adverse effects reported in this study, predominantly at 60 g Salatrim/day, were consistent with those documented during the clinic based studies (i.e. gastrointestinal disturbances and increases in serum transaminase levels). The authors considered that the effects on serum transaminase levels were transient with noticeable decreases in serum activities of AST and ALT occurring towards the end of the study period. We note, however, that convincing evidence of a decline in the activities of serum AST and ALT to baseline levels was not provided. Although increases in serum AST and ALT activities rarely reached clinical significance in the 28 day free living study, we note that there were concomitant increases in the activities of some liver function enzymes (i.e. AST and ALT) and reduced serum cholesterol documented in the clinicbased studies at 60 g Salatrim/day. There is limited published evidence to support the view that an increased load of high caloric materials such as proteins or sucrose in the diet may induce alterations in serum transaminase enzyme levels (Schimke, 1962; Porikos & Van Itallie, 1983).
- 9. The authors noted that none of the subjects in the 28-day free living study reported severe gastrointestinal effects, which might impair normal function. The effects were considered to be "mild" or "annoying". They considered that 30 g Salatrim/day would have little or no effect on the health of individuals. We *note* that complaints of adverse effects on gastrointestinal function persisted for at least 10 days in a small number of individuals at all dose levels, including two who consumed 30 g Salatrim/day.
- 10. There are a number of proposals concerning the mechanism(s) for the effects of Salatrim on gastrointestinal function. Increased stool weight and faecal water content as reported in the 4-day triple cross over study could have resulted in a bulking effect and hence may have contributed to the gastrointestinal symptoms. (Besselaar Clinical Research Unit, 1993). The authors have also proposed that the introduction of Salatrim, a poorly digested fat, into the diet may have caused transient gastrointestinal disturbance since similar effects have been documented following an abrupt increase in dietary fibre intake. (Finley *et al.*, 1994a; Pilch,

1987). The authors of the clinic-based studies have also speculated that the level of short chain fatty acids at high Salatrim doses (i.e. 60 g/day) might temporarily overwhelm the ability to utilise acetate which might be sufficient to induce some adverse gastrointestinal symptoms. (Finley *et al.*, 1994b). Overall, *we conclude* that there is no convincing explanation regarding the mechanism of the adverse gastrointestinal effects of Salatrims seen in the clinical studies. Additionally there is no information available regarding the likelihood of adverse gastrointestinal effects in children or individuals with compromised gastrointestinal tract function.

Consideration of the adequacy of the animal toxicological database

11. We *consider* that the animal toxicity studies were adequately conducted and can be used in the safety assessment of Salatrims. However, we *note*, that there are inadequate data available in respect of the potential effects of bolus doses of SCFAs on reproduction following their release from Salatrims during the metabolism of Salatrims in the gastrointestinal tract. We are *aware* that butyrate and propionate have been shown to have teratogenic potential *in-vitro* (Coakley *et al.* 1986, Brown *et al.* 1987). We reviewed the additional data provided by Cultor Food Science including calculations regarding potential blood levels of butyrate following consumption of a meal containing 30 g of Salatrim 4SO and *conclude* that additional pharmacokinetic studies to evaluate blood levels of SCFAs in volunteers following consumption of individual Salatrim products are required before any conclusions regarding the teratogenic risk of Salatrim(s) can be drawn. We *agree* that there is no requirement for additional mutagenicity studies or for the provision of carcinogenicity bioassays with Salatrim(s).

Consideration of the increases in aspartate aminotransferase and alanine aminotransferase documented in human clinical studies

12. We have considered all of the data available from the clinical studies with regard to the potential effects of Salatrim(s) on serum enzymes which can be used to evaluate potential adverse effects on liver function and have also considered the further information supplied by Cultor Food Science regarding an evaluation of the individual clinical chemistry for all of the clinical studies. We conclude that increases in both AST and ALT occurred in a higher proportion of individuals consuming 30 g or 60 g Salatrim per day for 28 days compared to controls, although only a few of these reported increases can be regarded as reaching the level of clinical significance. Whereas there were differences between individuals in respect of the magnitude of the increase in AST and ALT in response to the ingested dose level of Salatrim and also between that induced by different Salatrim products, we conclude that the evidence is consistent with a weak treatment related effect which did not appear to decline during the 28 day treatment period. The analysis of individual clinical chemical data for all of the clinical studies is complicated by the absence of detailed background information on the individuals included in the clinical studies and also, in respect of the 28 day study, by the identification of inconsistencies and transcription errors both in the original and published reports of this study. There was also additional evidence of concurrent increases in other serum enzymes consistent with liver dysfunction, such as alkaline phosphatase, lactate dehydrogenase and GGT, in a small number of individuals who ingested Salatrims.

Overall, we *consider* that a No Observable Adverse Effect Level (NOAEL) with respect to clinical chemical markers of liver function cannot be identified from the clinical safety studies undertaken with Salatrims and that no conclusions can be drawn with regard to the mechanism or biological significance of the Salatriminduced effects on AST and ALT.

13. We *consider* that there are insufficient data available to derive any firm conclusions regarding the reasons for an absence of effects on serum liver enzymes in the animal studies. We *conclude* that it would be appropriate to proceed on the basis that the effects on serum liver enzymes documented in the clinical safety studies were treatment-related and thus require additional evaluation, particularly with respect to the identification of an appropriate NOAEL. In this regard the discrepancies in the reporting of the results from the 28-day free living study limit the value of this investigation. We *recommend* that a suitable long-term clinical evaluation study of the individual Salatrims to be marketed should be undertaken with particular reference to the identification of a NOAEL.

Discussion and recommendations

- 14. We have, during our consideration of the questions raised by the ACNFP, evaluated all of the available toxicological and clinical safety studies on Salatrim and have considered the representations made by Cultor Food Science at the joint ACNFP/COT Working Group. The following two conclusions respond to the specific requests made by the ACNFP. An additional conclusion based on a consideration of all the toxicological and clinical data submitted to the COT is given in paragraph 15.
 - Animal toxicological data alone on Salatrims are insufficient to evaluate the proposed use of these materials as fat replacers. We *recommend* that additional pharmacokinetic studies to evaluate blood levels of SCFAs in volunteers following consumption of individual Salatrim products are required before any conclusions regarding the teratogenic risk of Salatrim(s) can be drawn.
 - ii) The clinical safety studies demonstrate a weak treatment related effect of Salatrims on serum levels of marker enzymes for liver dysfunction. There are insufficient data available to derive any firm conclusions regarding the reasons for an absence of effects on serum liver enzymes in the animal studies. The documented discrepancies in the reporting of the results from the 28 day free living study limit the value of this investigation with regard to evaluating the potential effects of Salatrims on liver function. We *recommend* that a suitable long-term clinical evaluation study of the individual Salatrims to be marketed should be undertaken with particular reference to the identification of a NOAEL for this effect.
- 15. Regarding overall conclusions, we *note* that evidence of adverse effects on gastrointestinal function and on marker enzymes for liver dysfunction in humans were reported following the consumption of 30 g Salatrim 23SO for 28 days and that there was clear evidence of adverse effects at 60 g/day regarding several Salatrim products. We are *concerned* that there would appear to be no margin of safety between these levels of consumption and the calculated potential intakes reported above in paragraph 2. Additionally children and individuals with compromised gastrointestinal function might be more susceptible to these particular effects associated with Salatrim consumption. We therefore *recommend* that the additional clinical studies requested in paragraph 14 (ii) should further investigate the potential effects of the Salatrim(s) to be marketed on gastrointestinal function with a view to also identifying a NOAEL for this effect.

December 1997

PRIVATE SALATRIM	short-chain source	long-chain source	molar ratio
family			
SALATRIM 4CA	tributyrin	hydrogenated canola oil	2.5:1
SALATRIM 4SO	tributyrin	hydrogenated soybean oil	12:1
SALATRIM 23CA	triacetin/tripropionin	hydrogenated canola oil	11:1:1
SALATRIM 23SO	triacetin/tripropionin	hydrogenated soybean oil	11:1:1
SALATRIM 32CA	tripropionin/triacetin	hydrogenated canola oil	11:1:1
SALATRIM 43SO	tributyrin/tripropionin	hydrogenated soybean oil	11:1:1
SALATRIM 234CS	triacetin/tripropionin/ tributyrin	hydrogenated cottonseed oil	4:4:4:1
SALATRIM 234CA	triacetin/tripropionin/ tributyrin	hydrogenated canola oil	4:4:4:1
SALATRIM 234SO	triacetin/tripropionin/ tributyrin	hydrogenated soybean oil	4:4:4:1

Table 1. Typical molar ratios of short- and long-chain acid sources used to prepare the SALATRIM family of edible oils*

* The SALATRIM family name defines the sources of the short-chain and longchain fatty acids with the numerals representing the carbon chain lengths of the short chain acids in decreasing proportion in the mix; the letters define the oil which provides the source of the long-chain fatty acids. (E.g. in SALATRIM 43SO tributyrin and tripropionin are the SCFAs and the LCFA source is hydrogenated Soybean Oil. The molar ratio of the mix that is used to prepare the SALATRIM is 11 parts tributyrin: 1 part tripropionin: 1 part hydrogenated soybean oil).

A listing of those products that have been used in safety evaluation studies is also given below. There are only very minor differences in composition between Salatrim products prepared from different long chain fatty acid sources. However, different batches of a product may have used differing molar ratios of the starting products.

Table 2. Materials used in metabolism and toxicity studies

Ames tests	4CA, 23CA, 23SO, 32CA, 234CA, 234CS	
In vitro mammalian tests	23CA	
In vivo bone marrow	234CA, 234SO	
micronucleus assays		
In vitro metabolism	4CA, 23CA, 32CA, 234CA	
(Porcine pancreatic lipase)		
Metabolism in rats	23CA	
90 day feeding studies (rats)	4CA, 23CA, 32CA, 23SO, 234CA, 234CS*	
(*and supplementary 17 day test of	effects on transaminases)	
28 day mini-pigs	23SO	
Effects on gut microflora: rats	23CA, 32CA	
Studies I & II in volunteers	23CA	
Studies III & IV in volunteers	23SO	
Free living study in volunteers	4SO, 23SO, 43SO	

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Annex III to Appendix III



Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

Statement for the Advisory Committee on Novel Foods and Processes on toxicological aspects of a submission on short and long chain triacyl glycerol molecules (Salatrims) – a family of low calorie fats submitted for approval under the EC Novel Food Regulation

Introduction

- 1. In 1997 we issued a statement (Committee on Toxicity, 1997) on specific aspects of a submission made to the Advisory Committee for Novel Foods and Processes (ACNFP) on Salatrims, a family of low calorie fat materials. We had been asked by ACNFP to comment on the toxicological aspects of the data provided at that time under the voluntary system that existed for the evaluation of novel foods.
- 2. We concluded that there were three areas of concern that needed to be addressed further, namely:
 - additional pharmacokinetic studies were required to evaluate blood levels of short chain fatty acids in volunteers following consumption of individual Salatrim products before any conclusions could be drawn regarding the teratogenic risk of Salatrims;
 - ii) a No Observable Adverse Effect Level (NOAEL) should be determined for effects of Salatrims on enzyme markers for liver dysfunction in humans; and
 - iii) a NOAEL should be determined for effects of Salatrims on gastrointestinal function in humans.
- 3. The EC Regulation on Novel Foods and Novel Food Ingredients was introduced in May 1997, after the initial consideration of Salatrims in 1995-1997.

As Salatrims were not on the market in Europe at that time, they are regarded as novel foods and therefore they require clearance under the Regulation before they can be sold in Europe. An application has now been made to the UK Competent Authority for such clearance (Cultor Food Science, 1999) and ACNFP has asked for our further advice on the additional information and analysis included in the submission to meet the concerns that we identified earlier.

4. Our first statement described the toxicological and clinical data available on Salatrims in 1997. This statement, which needs to be read in conjunction with our previous opinion, discusses the additional data and analyses provided in the submission made under the Novel Food Regulation in response to the concerns that we had identified.

Levels of short chain fatty acids and possible teratogenic risk

5. The Committee had previously expressed a concern that the release of butyric acid from Salatrim, which is rich in this short chain fatty acid, might be sufficient to cause a rise in plasma butyrate levels. This possibility needed to be examined in the light of *in vitro* data on possible teratogenic effects of high levels of butyric acid. A new study has been conducted (Pronczuk, Lipinski and Hayes, 1999) in which the post-prandial response to a

load of 30 grams (g) of butyrate-based Salatrim (known as 4SO) was investigated to determine, amongst other effects, whether free butyrate would reach the general circulation. Plasma was analysed for butyric acid at regular intervals up to 360 minutes after dosing and at no time could free butyric acid be detected.

6. The Committee was satisfied by these data.

Effects on enzyme markers for liver dysfunction in humans

- 7. The Committee had asked that further information be provided to enable a NOAEL to be set for the effects of Salatrims on enzyme markers of liver dysfunction seen previously in the free-living clinical study. The company has provided further statistical analyses of the serum enzyme data from this study and expert assessments of the implications of those statistical analyses.
- 8. Small, statistically significant increases were recorded in the mean activities of the enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) at the beginning of the exposure period in the free-living clinical study, although the mean values for the treatment groups did not fall outside the normal ranges for these enzymes at the laboratory conducting the study. The Committee noted that there was some concordance in the increases in liver enzymes AST and ALT within individuals and that some temporal trends were apparent. The Committee had also noted that it was possible that the individuals who withdrew from the study may have been atypical and that this could have contributed to the variability of the data.

However, the company submitted information that shows that those individuals who withdrew from the study, did so mainly because of adverse gastro-intestinal effects resulting from consumption of 60 g/day Salatrim. In addition, further analysis of the enzyme activities for those withdrawing from the study in comparison to those remaining shows that there were no significant differences in changes above baseline for serum hepatic enzyme activities whether or not those subjects withdrawing from the study were included.

- 9. In addition, data from a further study conducted by Nestel and colleagues (1998) were provided. In this five-week crossover study, following a low-fat control phase, subjects consumed diets containing margarine rich either in Salatrim or in palm oil ('palmitate'). These subjects were selected on the basis of their having an elevated blood cholesterol level and the study was designed primarily to provide information on effects of Salatrim on blood lipid levels. However, additional analyses of serum enzymes from blood samples taken pre-dose and at the end of each dietary phase showed that mean activities of AST and ALT, and other indices of hepatic function ((-glutamyl transferase, alkaline phosphatase and lactic dehydrogenase) were no different at the end of the Salatrim and 'palmitate' dietary phase in some subjects, which were of a similar magnitude to those seen in some subjects consuming Salatrim in the free-living clinical study described above.
- 10. The Committee concluded that consumption of high doses of Salatrim did result in slight increases in AST and ALT activities in serum, but noted that these increases were within the normal reference range. The further analyses of the enzyme data satisfied the Committee that there were no differences in the trends seen whether those withdrawing from the study were included or not. These enzyme changes, in the absence of any other indications of liver damage, were not considered to represent a clear toxic effect. The data from the five-week crossover study (Nestel *et al.*, 1998) provided reassurance of a lack of any clear

adverse hepatic effect. However, the Committee noted that the reported studies did not include investigations in children or in those with pre-existing liver disease.

Effects on gastrointestinal function in humans

11. The Committee had noted previously that gastrointestinal effects had been recorded in a number of subjects consuming Salatrim and had asked that further information be provided to enable a NOAEL to be determined. A further analysis of these observations was submitted by the company. The company suggested that the gastrointestinal disturbances reported was the consequence of sudden changes from an absorbable diet to one containing significant amounts of unabsorbable material.

Metabolism of Salatrims rich in short chain fatty acids might result in rapid release of cholecystokinin, which would lead to slow gastric emptying, nausea and bloating. Analysis of the reasons for subjects withdrawing from the study shows that adverse gastrointestinal symptoms (such as nausea, cramps and gas) were the predominant reason for withdrawal from the study in the 60-g/day Salatrim group. However, there was no clear evidence of any increase in the incidence of such effects at intakes of 30 or 45 g/day Salatrim.

- 12. The Committee considered that the gastrointestinal disturbances seen after consumption of high doses of Salatrim could be the result of individual intolerances, noting the considerable variation between individuals and their tolerance to fibre and other poorly digested substrates. Nevertheless, these effects were seen in a significant proportion of individuals after consumption of 60 g/day Salatrim and needed to be considered in the context of estimates for adults of a mean intake of 11 g Salatrim/day and of a 97.5th percentile intake of 33g Salatrim/day. Salatrims are intended for use in reduced calorie foods aimed at individuals choosing a diet for the control of weight (Cultor Food Science, 1999). The main target consumers would be adults over 16 years of age and the intake estimates therefore were derived only for adults using commercially available databases on UK food consumption in conjunction with information on the types of food in which Salatrim would be used and the likely levels of inclusion. The application under the Novel Food Regulation is restricted to use in confectionery and baked goods only.
- 13. The Committee was of the view that the gastrointestinal effects seen were likely to be linked to intolerances to large amounts of this material rather than any specific toxic effect. However, gastrointestinal effects might be more common in children because of their relatively higher nutrient requirement and dietary intake. The Committee further concluded that it was not possible to set any no effect level on the basis of such subjective end points.

Conclusions

On the basis of the new data and analyses now provided, the Committee concluded that:

- i) consumption of Salatrim did not result in any elevation in plasma butyrate levels and thus did not pose any teratogenic risk;
- ii) consumption of high doses of Salatrim did result in slight increases in AST and ALT activities in serum, although these increases were within the normal reference range. There were no differences in the trends seen whether those dropping out of the study were included or not. These changes in enzyme activities, in the absence of any other indications of liver damage, were not considered to represent a clear toxic effect. The data from the five-week crossover study in humans provided an additional reassurance of the lack of any clear adverse effect;

- iii) the gastrointestinal effects reported were likely to be linked to individual intolerances to large amounts of this material rather than to any adverse toxic effect. Furthermore, it is not possible to set any no effect level on the basis of such subjective end points.
- 15. The Committee noted that neither children nor those with pre-existing liver disease were included in the trial groups. However, the Committee understands that products containing Salatrim would be aimed at adults choosing a diet for the control of weight.

September 1999

COT Statement 1999/09

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Appendix IV

Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to Phytosterol esters

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

8 March 1999

Dear Mr Klepsch

Application from Unilever for marketing of yellow fat spreads containing additional phytosterol esters: initial assessment report from the Netherlands Competent Authority

The Competent Food Assessment Body for the UK Competent Authority, the Advisory Committee on Novel foods and Processes (ACNFP), has considered the initial assessment report produced by the Netherlands Competent Authority for approval of yellow fat spreads containing additional phytosterol esters and agrees with the recommendation that the approval be limited in the first instance to a maximum level of addition of 8%w/w. The UK Competent Authority has not considered the issues of nutrition labelling or of claims, which are subject to other national and European legislation.

In particular the UK Competent Authority agrees that:

- i) the possibility that some of the oils used in the production of the phytosterol ester ingredient might come from approved genetically modified plant sources does not raise any particular safety concerns and notes that such ingredients would be subject to the labelling requirements applicable to any ingredients derived from GM sources;
- ii) the consumption of phytosterol esters arising from the limited level of addition recommended by the NL Competent Authority will not have any significant adverse effects on the absorption of the fat-soluble vitamins D, E and K. Furthermore, the UK Competent Authority agrees that there may be an adverse effect on the absorption of carotenoids and therefore agrees with the recommendation from the NL Competent Authority that the level of addition of phytosterol esters to yellow fat spreads be restricted in the first instance to a maximum of 8%w/w.

The UK Competent Authority also welcomes the fact that the company will be carrying out follow up studies in human volunteers and agrees that the provision of such additional data would be essential before any decision could be taken to increase the level of addition of phytosterol esters to yellow fat spreads or to widen the range of food products in which this ingredient could be used;

iii) the data provided from the toxicological studies carried out in animals, including a multigeneration study in the rat, as well as clinical studies in human volunteers, support the safety in use of this ingredient, as described in the application; iv) there should be clear labelling of the phytosterol ester ingredient in food products so that the very small number of people with an inborn error in the metabolism of phytosterols can avoid such products. The UK Competent Authority accepts that food products containing phytosterol esters will be aimed at the particular section of the population that is trying to control it's blood cholesterol levels by dietary means. Nevertheless the UK Competent Authority is of the opinion that there are sections of the population for whom reduction in blood cholesterol levels is not nutritionally applicable, and in whom vitamin A status may not be optimal, that is children under the age of 5 years and lactating women. The UK Competent Authority is therefore of the opinion that this information ought to be made available to the public and suggests that this might be achieved via GPs and other health professionals (such as midwives and health visitors). The UK Competent Authority also recommends that information regarding the recommended daily intake of phytosterol ester-containing products ought to be available to consumers on the packaging of the product.

Finally the UK Competent Authority would ask that the company be reminded that any clearance of this ingredient under the Novel Foods Regulation 258/97, and any labelling requirements thereof, does not prejudice the need to comply with existing national and European food labelling requirements on nutritional composition and on any claims made, including the requirement to provide scientific evidence necessary to justify any such claims.

I am copying this letter to all other Member State Competent Authorities.

Yours sincerely

Mrs S J Hattersley

Food Safety Policy Division (D) Department of Health UK Novel Foods Competent Authority

Appendix V

Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to Nangai nuts (*Canerium indicum* L)

Your reference:

Our reference: NFB 320

3 June 1999

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

Dear Mr Klepsch

Application under EC Regulation 258/97 – Nangai nuts

The Competent Food Assessment Body for the UK Competent Authority, the Advisory Committee on Novel Foods and Processes (ACNFP), has considered the initial assessment report from the French Competent Authority on the marketing of Nangai nuts in the Community. The UK Competent Authority wishes to raise objections in relation to a number of issues.

The UK does not accept that the apparent history of safe use in the Pacific region provides sufficient reassurance for consumers in the Community. Firstly there is no evidence of a robust system in the area for recording possible adverse reactions to foods. Secondly, and perhaps more importantly, there is evidence that there is a lower incidence of adverse reactions such as allergy in areas where a food is a more common component of the diet. There is also concern that the toxicological profile of the nuts has been inadequately investigated. While there is a little information on extrinsic factors which may have safety implications, there is little or no data relating to testing of intrinsic factors.

Further information is requested on the following aspects:

- a) a more detailed account of the agricultural production system, including any inputs and controls;
- b) a more detailed account of the post harvest production system, including details of QA/QC procedures employed and their regularity. The present description suggests these may not be sufficiently robust;
- c) consideration of the potential hazards which may arise in the production procedure e.g. possibility of mycotoxin contamination (over and above those tested for) or other environmental contamination (microbiological and chemical) which may be particularly of relevance to the indigenous area and mode of cultivation/production. This should include details of the testing protocols to ensure these are appropriate;

- d) a more detailed specification, including data on the natural variation of the parameters (both compositional and of possible contaminants) measured. This would require analysis of several more batches, over and above the single batch data which has been supplied;
- e) it is envisaged that the nuts will be imported and then marketed in roasted form. The implications of subsequent processes on the safety for consumers would need addressing in more detail;
- f) a need for toxicological studies in animals and allergenicity studies has been identified to address potential safety issues on the marketed product, together with the possible need for specific labelling.

Yours sincerely

Nick Tomlinson Additives and Novel Foods Division MAFF

Appendix VI

Letter to the European Commission containing UK Competent Authority comments on data presented in an application relating to PrimaDex – High Molecular Weight Bacterial Dextran

Your reference:

Our reference: NFB 340

Mr P. Deboyser Commission of the European Communities DG III Rue de la Loi 200 B1049 Brussels Belgium

23 September 1999

Dear Mr Deboyser,

Bacterial Dextran – Puracor (B)

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 Belgian Competent Authority for the placing on the market of High Molecular Weight Bacterial Dextran (PrimaDex). The UK Competent Authority does not wish to raise any objections to the marketing of this product.

Yours sincerely

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

Appendix VII

Letter from the Department of Health to health professionals regarding phytosterol esters and phytostanol esters (Benecol)

To: Royal College of General Practitioners
Royal College of Physicians
Royal College of Pathologists
Royal College of Midwives
Community Practitioner and Health Visitor's Association
Royal College of Nursing
Royal Pharmaceutical Society of Great Britain
British Medical Association
National Poisons Information Service
Food and Drink Federation
British Retail Consortium
LACOTS

7 January 2000

Dear Sirs

Cholesterol-Lowering Ingredients in Foods – Nutrition Advice to Subgroups of the Population

I am writing to you about recent developments in foods which claim to provide additional health benefits.

You may be aware that foods containing additional amounts of ingredients, such as phytostanol and phytosterol esters, which are claimed to help to lower blood cholesterol levels, are being developed. An example is the Benecol (phytostanol esters) range of food products, which are being introduced into the UK.

Phytosterol and phytostanol esters are compounds naturally present at low levels in vegetable oils and foods derived from them, and therefore form part of the existing diet of most people. However, consumption of high levels of these ingredients may interfere with the absorption of certain fat-soluble dietary nutrients, including some vitamins.

There are no concerns about the safety of these products for any population group. However, there are certain groups of the population for whom reduction of blood cholesterol levels is not considered to be nutritionally appropriate and in whom vitamin A status may not be optimal. These are pregnant and lactating women and young children under the age of 5 years. The independent committees of experts that advise Government on novel food and food labelling issues (the Advisory Committee on Novel Foods and Processes – ACNFP – and the Food Advisory Committee – FAC) have therefore recommended that, in addition to labelling of the food products themselves, information should be given to these population groups, or their carers, that foods that claim to help to lower blood cholesterol levels are not appropriate for them.

The committees recognised that health professionals such as GPs, midwives and health visitors, who already give nutritional advice to these population groups, would be well placed to provide

this information. We are therefore writing to you to ask if you would pass this information to your members and enlist their co-operation in providing this advice to the relevant subgroups of the public.

General information on the control of novel foods under the European Commission Regulation 258/97, and the safety assessment procedures for novel foods may be obtained from the ACNFP Secretariat at MAFF, Room 239, Ergon House, 17 Smith Square, London SW1P 3JR.

If you have any queries relating to this letter, please contact:

Mrs S J Hattersley DH JFSSG Room 653C Skipton House 80 London Road Elephant and Castle London SEI 6LH

Yours sincerely

Dr Pat Troop Deputy Chief Medical Officer

Appendix VIII

Statement on the studies conducted at the Rowett Research Institute on potatoes genetically modified to produce the snowdrop (*Galanthus nivalis*) lectin

Introduction

The Committee has reviewed a number of documents relating to the studies carried out at the Rowett Research Institute on potatoes genetically modified to produce the snowdrop (*Galanthus nivalis*) lectin (1–5). The Committee had not been asked to assess the safety of the particular lines of genetically modified (GM) potatoes tested in these studies nor was it intended that these GM potatoes would be released onto the market. However, given the way the results of the studies were presented, via the media rather than the peer review process, and that they appeared to raise a number of generic questions about the safety assessment of GM foods, the Committee considered it essential that it should have an opportunity to review the studies. Unfortunately, the original study reports were not made available to the Committee and it had to rely on a number of documents that were already in the public domain.

Background

A series of studies had been carried out in rats using both raw and cooked GM and non-GM potatoes. In addition, raw and cooked potatoes spiked with either the snowdrop lectin or the jack bean lectin, concanavalin A (ConA) were also tested. The potatoes were included in the diet and were fed either for a period of 10 days or 110 days. Body weight gain was monitored throughout each study and at the end of each study organ weight measurements were carried out. In one of the short term studies (10–day) tissue samples were taken from the gastrointestinal tract of rats fed either the GM potato (raw and cooked) or potato (raw and cooked) spiked with the snowdrop lectin, for histological examination. In addition, an assessment of immune function was performed in some of the studies using the lymphocyte proliferation assay.

Results

It had been widely reported in the media that the GM potatoes tested in these studies had produce an adverse effect on growth and immune function in rats. The histological findings were similarly publicised as indicating that the GM potatoes produced adverse effects in the gastrointestinal tract.

Given the nature of these findings, the Committee asked that the available data be referred to the Committee on Toxicity (COT) for advice on the significance of these findings. The COT's advice is detailed in the attached statement.

Having considered all of the available data, the ACNFP considered that the studies were badly designed and did not appear to be hypothesis-led. Some changes in body weight and organ weight were evident in some of the studies. However, although attempts had been made to ensure that the potato-supplemented diets were nutritionally adequate, this had not been achieved. The Committee noted that the nutritional adequacy and nutrient density of the diet could have an effect on body weight and organ weight. In addition, the effects of dietary restriction due to palatability problems did not appear to have been taken into consideration in the studies and this could also have been responsible for the weight changes observed as well as the histological findings in the

gut. The Committee questioned the appropriateness of using raw potatoes in the studies, given that potatoes were not normally consumed in this way, and noted that feeding rats raw potato starch was known to produce alterations of gut morphology. The Committee indicated that further work was necessary in order to determine the nature of the changes observed in the GI tract.

The Committee noted that there was wide variation in the results of the lymphocyte proliferation assay that called in the question the reliability of the assay in this instance. However, the Committee was of the view that it was not possible to draw any conclusions on the effects of the GM potato on immune function based on the results of this assay alone.

Conclusions

The Committee agreed that given the concerns expressed about the design of the studies and the nutritional quality of the potato-supplemented diets used in the studies, no meaningful conclusions could be drawn on the effect of feeding rats GM potatoes expressing the snowdrop lectin. In addition many of the adverse effects seen occurred in rats fed potatoes spiked with the ConA lectin. The results of the studies illustrated the need to assess the safety of GM foods on a case-by-case basis.

May 1999

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Committee on toxicity of chemicals in food, consumer products and the environment

Statement on studies of potatoes genetically modified to produce a foreign lectin



Introduction

- 1. The Committee was asked to provide advice to the Advisory Committee on Novel Foods and Processes (ACNFP) on the toxicological aspects of studies which had been carried out at the Rowett Research Institute. These unpublished studies involved the administration to rats of various diets, some containing potatoes (both raw and cooked) either with or without the addition of a non-potato lectin or potatoes which had been genetically modified to produce the snowdrop (*Galanthus nivalis*) lectin.
- 2. These studies had received considerable publicity following statements about adverse effects on the rats made on a television programme. Accordingly, the Secretariat of the ACNFP had sought to obtain copies of detailed scientific reports relating to these studies. It had only been able to obtain certain documents that were already in the public domain and a manuscript submitted for publication by Dr Stanley Ewen and Dr Arpad Pusztai. The documents that were considered by the Committee on Toxicity are listed below.
- 3. The Committee was particularly asked to consider the significance of:
 - the effects reported on the body and organ weights of the rats;
 - the results of the lymphocyte proliferation assay; and
 - the histological changes reported in the gastrointestinal tract.
- 4. Dr Pusztai and Dr Ewen were invited to attend the meeting of the Committee. Unfortunately, only Dr Ewen was able to be present. He made a presentation to the Committee on the histopathology of the gastrointestinal tract of rats from one of the relevant studies. Also he answered questions from Committee members during the subsequent discussions.

The Committee's discussions

- 5. In the course of their consideration the Committee indicated that certain important information about the studies was not provided in the documentation available. Although Dr Ewen was able to provide additional details on the histopathology he was not able to help with questions relating to the design of the studies or matters relating to the body and organ weight changes and the lymphocyte proliferation assay.
- 6. In response to a question, the Committee was informed that it was understood that the genetically modified lines of potatoes used in these studies were never intended for release on the market and that no application for such release had been made to the ACNFP.

Body and organ weight changes

7. The Committee recognised that an exact knowledge of the composition of the diet and the use of appropriate statistical methods were crucial to the interpretation of the changes in body and organ weights that had been recorded in the studies. The known adverse effects on the health of laboratory rats of raw potato starch in the diet were pointed out. In addition, the importance of minor changes in composition and palatability of the diet in

determining the body weight in the rat were stressed. Although it was clear that attempts had been made to ensure that the animals had received an appropriate diet, there was a lack of critical information that would allow the Committee to satisfy themselves that this had been achieved.

Lymphocyte proliferation assay

8. The variability of the results from this assay has been described in the report of the Audit committee of the Rowett Research Institute (Bourne *et al.*, 1998). The Committee noted that this variation meant that the studies could not be considered in isolation. Further, it was considered necessary to relate any immune system changes to changes occurring in other organs of the rats.

Histopathology

9. Dr Ewen made a presentation of the histopathology of the gastro-intestinal tract. In this he showed slides recording changes to the thickness of the mucosa in the stomach and sections of the small intestine occurring after feeding of diets containing genetically modified potato. A common feature was elongation of the crypt and villi of the jejunum and ilium. The Committee enquired as to whether measures that would discriminate between hypertrophy and hyperplasia had been made. They were informed that this had not yet been done. The histopathology related only to the gastrointestinal tract of the rats from one of the studies, it was pointed out that it would be usual for a toxicology study to have incorporated a full examination of all the major organs. The Committee was of the view that this would have provided an opportunity for seeking an explanation of any changes to the immune system or of organ weights.

Conclusions

- 10. The Committee expressed its concern about a number of aspects of the design of the studies as were apparent from the papers submitted to it. These included the number of rats in the experimental groups and the lack of demonstration that the diets used were nutritionally adequate and that they contained comparable amounts of materials, such as potato starch and natural potato lectins, both of which are known to affect the gastrointestinal tract. It appeared that a limited set of studies contained too many variables to draw any definitive conclusions as to the safety of the particular GM potato line studied.
- 11. It was agreed that the studies could be used to provide an indication of the investigations and procedures that would be needed in any future work in this area. However, these studies could not be used by themselves for defining the effects of potatoes containing the transgene for the Galanthus nivalis lectin on the rat.

May 1999 [COT Statement 1999/00]

Appendix IX

Minutes of the joint meeting of ACNFP and ACAF: 1 December 1999 Mary Sumner House, London

Present

ACNFP Professor J Bainbridge – Chair Dr P Dale Dr M Gasson Professor I Rowland Mrs E Russell Dr N Simmons Professor H F Woods Dr J Bell – MAFF Assessor Mrs S Hattersley – IESSG / DH Secretar

Mrs S Hattersley – JFSSG/DH Secretary Mr N Tomlinson – JFSSG/MAFF Secretary Mr A Wotherspoon – Secretariat (JFSSG/MAFF) Mr K Woodfine – Secretariat (JFSSG/MAFF) Miss T Boshier – Secretariat (JFSSG/MAFF) – Minutes

<u>ACAF</u>

Professor P Thomas – (Chair) Dr I Brown Mr J Cheetham Dr A Chesson Mrs G Davies Mr P Foxcroft Dr J Heritage Mrs F Hodgson Mr R Moore Mr A Peddie Dr H Raine Dr D Rice Professor I Shaw Dr M Stringer

Dr R Burt – JFSSG/MAFF Assessor Mr D Renshaw – JFSSG/DH Assessor Professor C McMurray – DANI Mr B Knock – Secretariat (JFSSG/MAFF) Mrs K Dell – Secretariat (JFSSG/MAFF) <u>In attendance</u> Dr R Smith – JFSSG/MAFF Dr P Burrows – DETR (ACRE Secretary) Mr R Vaz – National Food Administration, Sweden

1. Introductory remarks

- **1.1** Mr R Vaz was welcomed as an observer from the National Food Administration of Sweden.
- **1.2** It had been agreed that Professor Bainbridge, the ACNFP Chairman, would chair the first joint meeting of ACNFP and ACAF. She gave a brief introduction to the history of the ACNFP and explained the way in which it operates. She emphasised in particular the ACNFP's commitment to greater transparency and the procedures that were being developed to achieve this.
- **1.3** The Chairman went on to suggest that while there were a number of issues that were distinct to each committee, there were others which were of relevance to both, such as the size of sample required to obtain statistically valid data and the role of animal/toxicological studies in safety assessment, and where it would be important to explore the possibility of taking a common approach.
- **1.4** The ACAF Chairman was invited to make some introductory remarks on behalf of ACAF. He explained the background to the remit of his committee and expressed the wish to learn as much as possible from the ACNFP's experience in dealing with the GM applications. He agreed that in areas of common interest the two committees should work as closely together as possible.

2. Approaches to assessing the safety of GM materials for use as human food or animal feed

- **2.1** This paper formed the main item for discussion at the meeting. It gave a detailed account of the ACNFP's approach to GM assessments and described the EC guidelines which exist for bioproteins used in animal feed, the only area of animal feed for which a formal safety assessment was required.
- **2.2** The paper suggested that, while the type of materials used in animal feed and the level of exposure may differ from those for human food, in principle the approach to assessing the safety of human food appeared to be equally valid for animal feed. This was based on the concept of substantial equivalence with the need for particular studies (including toxicological work) being decided on a case-by-case basis.
- **2.3** The paper went on to invite the Committees to discuss the system of safety assessment for GM foods, the ACNFP's experiences in the area, and the applicability of the approach to the consideration of GM feed.
- 2.4 Members first looked at the relevance of the concept of substantial equivalence with respect to animal feed assessments. They recognised that it had been the practice within the feed industry to assess feed materials from non-GM crop varieties for some time. This focusses on the effect that any differences from existing crops might have on the ability of target animals to thrive. Where there was little difference, minimal or no testing was necessary. In other cases, feeding trials were carried out.

- **2.5** It was pointed out that the present emphasis for such trials was on nutritional performance rather than safety, although the animals are monitored for their general health status. These trials were conducted on a different basis to those undertaken in classical toxicology tests in that little, if any, pathology was carried out.
- 2.6 In the case of novel feed materials, non-novel counterparts were almost always available as most new crops were variants of existing crops. Consideration needed to be given however to the type of physiological system in the animal and its influence on degradability of the feed e.g. feeding trials carried out with monogastrics would not be directly applicable to ruminants. Such factors highlighted the need to assess each product on a case-by-case basis.
- 2.7 The EC guidelines on novel additives and bioproteins in feed were examined. These indicated the types of information and a list of studies that should be provided in support of new products, as well as specific guidance on target animal studies. Where GM technology is used, common procedures for assessment of potential risks have evolved which differ very little in principle to those adopted for the assessment of food. These concentrate on three aspects:
 - Molecular biology of product/DNA insert etc
 - Potential transfer to the environment
 - Nature of expression products (i.e. of a gene expressed in an alternative host) investigated through toxicological studies.
- **2.8** In relation to food safety, it was recognised that the starting point of the assessment by each of the Committees is different. ACNFP is concerned with the safety of (a range of types of) novel foods as consumed whereas ACAF will examine the implications for the animal and their products from the consumption of novel feeds.
- **2.9** In view of the inherent difficulties in running meaningful animal toxicological studies, the need to have a clear scientific justification for carrying out animal testing was stressed as an important consideration. Tests should be performed to provide answers to specific questions and to confirm or refute particular expectations. However, it was recognised that, as with conventionally bred plants, animal studies cannot be expected to, and will not provide, all the answers. Their main function in respect of animal feed would be to continue to be able to test for nutritional adequacy.
- 2.10 Members agreed that the major issue facing them was that of the unpredictable, inadvertent changes that might occur in modified plants (and indeed newly bred varieties of non-GM plants) and the extent of the testing that can be performed to address these. They were aware that it was not possible to ensure the absolute safety of any product, be it GM or non-GM. It is a multi-faceted problem for which endless data could be collected. However, it is the interpretation of the data and its implications that is the key element in any rigorous safety assessment.
- 2.11 In conclusion it was agreed that each application for a novel food or feed needed to be assessed on a case-by-case basis. It was clear however, that the concept of substantial equivalence is and would be very important to both Committees. Some members asked for more information on the applicability of substantial equivalence. The ACNFP will keep ACAF informed of developments in this area. The application of substantial equivalence to date had proved an important tool in food safety assessment but the new generation of products would create new challenges. New developments in methodology, as recently

reviewed by the ACNFP, will be important for the future. The two Committees agreed to continue to consult on common issues as these arise.

3. Specification for research project on the fate of GM material fed to chickens

- **3.1** This paper provided a draft specification for a proposed research project investigating the fate of transgenic material in chickens. Broilers present an ideal medium for a study such as this because of their size and relatively short production cycle. It is not a safety study on the GM material involved, which has already been fully assessed. As highlighted in a recent Royal Society report, evidence to date indicates that little (if any) DNA survives processing and passage through an animal's digestive tract and any that does, does not end up in meat, milk or other animal products.
- **3.2** The results of the project will be presented to the Committees for their consideration and therefore members were invited to comment on the proposal before the project starts.
- **3.3** The Committees agreed that this was a useful piece of research but that attention should be paid to the feeding regime with respect to the relevance of the data obtained. However, it was recognised that some atypical feeding would be necessary and was acceptable since the purpose was to investigate whether and to what extent plant genetic material may be incorporated into mammalian cells. Also the investigation would involve searching for what is very likely to be a rare event and some specific addition of DNA to samples (positive control) would be required to augment the levels present.
- **3.4** Some potential complications were highlighted, such as problems with digestion and the possible need to spike the feed in order to overcome any issues with the sensitivity of the proposed analysis. The need for proper controls was also stressed. It was agreed that the proposal would be reviewed in the light of the members' comments. Both Committees would be interested in how the project progresses and in receiving and discussing the results.

4. Future liaison between the committees

4.1 It was agreed that the Committees would arrange to meet as the need for discussion on issues of common interest arose.

ACNFP Secretariat JFSSG/MAFF December 1999

Торіс	Report	Page	
ACNFP/ACAF – joint meeting	1999	16	
Amylolytic yeast	1993	4	
	1992	16	
Antibiotic resistance markers	1998	12	
	1995	18	
	1994	3	
	1993	13	
	1991	17	
	1990	10	
Bacillus laterosporus	1994	7	
,	1993	7	
Bakers veast - GM	1990	2	
bukers yeast Givi	1990	2	
	1909	Ζ	
Benecol	1999	13	
Calcium-L-Mefolinate	1999	12	
Camelina oil	1998	10	
Cereal fractions	1999	4	
	1998	6	
Chaparral	1993	6	
Cherry and apricot kernel oils	1993	10	
	1992	12	
Chicory – GM	1999	10	
5	1998	8	
	1996	12	
Chymosin - ex E coli	1992	9	
	1991	10	
– ex Asn niger var avamori	1990	3	
- ex K lactis 19903 from GM source	1989	6	
	1707	0	
Code of conduct	1999	31	
COMA (ACNED of hericit	1998	28	
COIVIA/ACINFF aa hoc joint	1009	11	
working group	1998	11	

Торіс	Report	Page	
Consumer concerns – workshop	1991	16	
	1990	10	
COT – joint meeting	1998	13	
	1997	14	
	1991	15	
Review of Putztai's potatoes	1999	14	
Cottonseed – genetically modified			
for herbicide tolerance	1999	7	
	1998	6	
	1997	12	
	1996	5	
Cottonseed – genetically modified			
for insect resistance	1999	7	
	1998	6	
	1997	11	
	1996	5	
Crossing of two GM plants	1999	15	
Culture collections	1995	18	
Dextrans – in fructose syrup	1990	3	
	1989	6	
- in clinical nutrition products	1993	6	
EC Regulation on Novel Foods	1999	1	
-	1998	1	
	1997	3	
	1996	19	
	1995	19	
	1994	11	
	1993	15	
	1992	21	
Education in biotechnology	1991	18	
Enterococcus faecium	1995	3	
Enzyme hydrolysis of whole grain	1991	6	
	1990	5	

Торіс	Report	Page	
Enzymic modification of vegetable oils	1995	11	
,	1993	4,5	
	1992	10	
	1991	12	
	1990	5	
Fruitrim	1998	10	
Gene transfer – IVEM Report	1999	15	
– MAFF research	1998	12	
Germanium	1991	11	
	1001	0	
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	
0	1990	9	
	1989	9	
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	
Human volunteer studies	1999	13	
Increasing the openness of the ACNFP	1999	17	

Торіс	Report	Page	
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	1999	19	
	1998	15	
	1997	16	
	1996	19	
	1995	19	
	1994	11	
Labelling – products from			
genetically modified sources	1999	19	
8	1998	15	
	1997	16	
	1993	13	
Lactobacillus GG	1993	10	
	1992	12	
	1772		
Lipase ex <i>Asp oryzae</i>	1996	9	
	1995	14	
	1994	7	
	1992	17	
Low α – 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	
Lyprinol	1999	12	

Торіс	Report	Page
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	1999	29–31
	1998	25–28
	1997	26–28
	1996	28–30
	1995	28–30
	1994	23–25
	1993	25–27
Nangai nuts	1999	11
Novel fat replacer – structured triglycerides composed of mixtures of		
short & long-chain fatty	1007	
acids	1997	8
	1996	11
a 111 a 1	1995	15
– egg & milk proteins	1989	/
– cocoa butter replacer	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
Oilseed rape – genetically modified		
for herbicide tolerance	1999	7
Oil from GM oilseed rape	1995	3,5,6
	1994	4

Торіс	Report	Page	
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	1999	9	
	1998	9	
Phytosterols	1999	8	
Pollen from GM plants in honey	1992	11	
	1991	13	
	1990	9	
Polyporus squamosus mycelial protein	1993	8	
Polysaccharide fat replacers	1997	9	
Post market monitoring of novel			
foods – ACNFP Sub-Group	1999	18	
-	1998	14	
Potatoes genetically modified			
for insect resistance	1997	12	
GM potato research at Rowett			
Institute	1999	14	
	1998	12	
Quinoa	1995	16	
	1992	15	
	1991	13	
	1990	8	
Radicchio rosso	1999	10	
Riboflavin from GM Bacillus subtilis	1996	7	
Risk assessment: role of			
Advisory Committees	1998	11	
Royal Society statement on GM			
plants for food use	1998	12	

Торіс	Report	Page	
Salatrims	1999	5	
Seminar on allergenicity	1999	16	
Seminar on novel techniques	1999	16	
Single cell protein	1997 1996	10 12	
	1770	12	
Enzymatically partially	1996 1995	11 15	
depolymensed polysacchande	1995	15	
Soya beans – herbicide resistant	1994	5	
Statistically valid data to support			
safety clearance of crops products	1998	10	
Stevia rebaudiana Bertoni	1999	10	
	1998	8	
Substantial equivalence	1999	1	
	1998	1	
Sugar beet fibre	1992	17	
Taste trial – guidelines	1992	9	
	1991	10	
– beers from GM yeasts	1990	2	
CM tomotoos	1989	5	
– GM tomatoes	1990	5	
Processed products from GM tomatoes	1999	6	
	1997	7	
	1995	9	
	1994	3	
GM Tomatoes to be eaten fresh	1995	8	
Toxicological assessment of novel foods	1998	11	
Transgenic animals	1994	9	
	1992	7	
	1991	7	
	1990	7	
	1989	8	
– ethics group	1993	9	

Торіс	Report	Page	
Transparency of the ACNFP	1999	17	
	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	

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