ACNFP

Advisory Committee on Novel Foods and Processes

Annual Report 2007

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.'

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Foreword

This is the nineteenth annual report of the Advisory Committee on Novel Foods and Processes (ACNFP) and the fifth under my chairmanship.

The primary role of the ACNFP remains the safety assessment of novel foods and processes in line with the EU procedures set out in Regulation (EC) No 258/97. However, as is reflected by the contents of this report, the Committee continues to have a role in advising the Food Standards Agency on matters related to genetically modified (GM) foods.

In order to fulfil its role, the ACNFP has an impressive membership with highly qualified expertise in a wide range of scientific disciplines as well as two consumer representatives and an ethicist. I would like to take this opportunity to thank my fellow Committee members for their expert advice, hard work and support throughout the year. At this time it is also appropriate for me to acknowledge the contributions of Miss Jill Brand, Professor Ruth Chadwick, Mr Neville Craddock, Dr Peter Lund, and Professor Alan Malcolm whose terms of appointment came to an end in December 2007.

This report illustrates the extent and variety of the applications that have been considered by the Committee and the hard work of the secretariat, whose assistance and support is invaluable to the effective operation of the Committee.

Professor Mike Gasson
2008

Introduction

This is the nineteenth annual report of the work of the Advisory Committee on Novel Foods and Processes (ACNFP). The remit of the ACNFP can be found in **Appendix I**.

In 2007, the ACNFP considered a number of applications made under the Novel Food Regulation, details of which are in Sections 1, 2 and 3 of this report. These have been split into 3 sections; full applications submitted to the UK Competent Authority; substantial equivalence applications submitted to the UK Competent Authority and applications submitted to other Member States. Those topics discussed during 2007 that were continuations of previous work are indicated as such. Section 4 provides information on notifications submitted to the European Commission.

Other issues that the Committee has dealt with during 2007 are described in section 5 of the report. A cumulative index of topics considered in the ACNFP's annual reports from 1989 to 2007 can be found in Section 9. Hard copies of previous reports can be obtained from the Committee Secretariat (see section 7). Alternatively all ACNFP reports, as well as other information on the Committee, can be found on its web pages.[1]

[1] www.acnfp.gov.uk

1 Full applications submitted to the UK Competent Authority

1.1 Echium oil

This application from Croda Chemicals Ltd. was described in the 2006 Annual Report.

Following the Committee's request for additional information, the applicant provided details on the potential interaction of the ingredient with anti-coagulant medication, the estimated daily intake of the ingredient, labelling, HACCP, nutritional implications and the method used to carry out protein analysis on the novel ingredient.

At the January meeting, the Committee was content with the majority of the additional information provided by the applicant but noted that the nutritional implications of the novel ingredient were not addressed, as the applicant had not considered existing ingredients that might be displaced from the diet, such as oily fish, for which a nutritional benefit has been established.

The Committee also remained concerned that protein profiling information was not provided and considered that the protein extraction method used was not adequate because the proteins in the final product were unlikely to be soluble in water. In addition, the oil refining process was highly likely to denature and modify the proteins, which would affect the reliability of the Bradford method.

At the March meeting, the Committee considered further information on these two issues. Members were content with the updated protein analysis which showed low protein levels. Members were also content that the novel ingredient would not be nutritionally disadvantageous for the consumer if it is marketed as an alternative (non-fish) source of polyunsaturated fatty acids (PUFA's).

Following this meeting, the Committee's initial opinion was finalised and forwarded to the Commission for consideration by other Member States in July 2007. A copy of this opinion is attached as **Appendix II**.

1.2 Ice structuring protein from GM yeast

This application from Unilever was first described in the 2006 Annual Report.

Following the Committee's request for additional information, the applicant provided additional details on a number of outstanding issues which were considered at the January meeting. Members accepted that the applicant had demonstrated that the glycosylated form of the ISP had no function, that the product underwent minimal purification in order to maximise its functional activity and that there were no secondary integration sites in the genetically modified yeast that is used to manufacture the ISP preparation.

In response to a query as to whether the product should be labelled as being derived from a GM source, the Secretariat advised that legislation on GM foods (and therefore mandatory labelling) did not apply to this type of product. The Committee accepted this view but nevertheless recommended that the applicant should provide information to consumers about the manufacturing process, either through information provided on food packaging or other routes. Although the Committee accepted that refined fermentation products obtained from GM microorganisms were not currently highlighted in this way, there was substantial consumer interest in foods produced using GM technology and some aspects of the novel ingredient made it a special case, such as the use of a synthetic gene sequence and the presence of a significant proportion of cellular by-products from the GM yeast.

Following a significant number of comments from the public after the publication of the draft opinion, the Committee emphasised at its July meeting that information regarding the nature of the ingredient should be readily accessible and the applicant should not rely solely on websites, noting that a significant proportion of households in the UK do not have internet access. Members also recommended that the applicant should review the supporting information that they intended to provide, as the information currently available in other (non-EU) markets did not fully describe the product, for example in relation to residues of yeast by-products.

The Committee's initial opinion was finalised and forwarded to the Commission for consideration by other Member States in August 2007. A copy of this opinion is attached as **Appendix III**.

1.3 Glucosamine hydrochloride from *Aspergillus niger*

This application from Cargill was first described in the 2006 Annual Report.

At the January meeting, the Committee was invited to review information provided by the applicant in response to concerns raised previously regarding the possible presence of protein and the potential effect of consumption of the product by individuals with Type 2 Diabetes.

The Committee was not satisfied with the information regarding the presence of protein in the product, and requested that the applicant consider alternative testing methods. Members remained concerned about the possible effect that long-term consumption of the product may have in individuals with Type 2 Diabetes, noting that foods containing the ingredient would be attractive to older consumers who in demographic terms were the most likely to suffer from Type 2 Diabetes. The Committee considered that any risk to diabetics was difficult to manage through labelling as some diabetics are unaware they have the disease. Concerning labelling, the Committee advised that consumers should be informed of the fungal source of the product.

The applicant's further response was reviewed at the May meeting. The Committee accepted that an additional protein analysis, performed using mass spectrometry, indicated that the product was unlikely to contain levels of protein that would elicit an allergenic response. However, the Committee considered that the expert review provided by the applicant did not answer their earlier concerns regarding the potential of the novel ingredient to alter glucose metabolism, which would be of concern to individuals with diabetes. Members accepted that glucosamine is currently sold in the UK in the form of dietary supplements, but any possible effect in diabetics would be of greater concern if it was being added as an ingredient to a range of foods, since adverse reactions were less likely to be picked up by clinicians than if the glucosamine was being consumed as a food supplement.

The Committee's draft initial opinion, which concluded that additional assessment was required in relation to the potential effect of glucosamine on glucose metabolism, was published for comment. A member of the public raised the possibility that the acid hydrolysis stage of the manufacturing process could give rise to the presence of chloropropanols such as 3-monochloropropane-1,2,-diol (3-MCPD). The Committee accepted that applicant's response that 3-MCPD, if present, would be removed during the purification process.

The Committee's opinion was forwarded to the Commission for consideration by other Member States in September 2007. A copy of this opinion is attached as **Appendix IV**.

1.4 Baobab dried fruit pulp

This application from Phytotrade (Africa) for the authorisation of the pulp of the Baobab Fruit was first considered at the January meeting. Baobab dried fruit pulp is obtained from the fruits of the baobab tree (Adansonia digitata). The baobab fruit comprises of a very hard outer shell, whitish powdery pulp and kidney-shaped seeds. The shell and the seeds are removed and discarded. The pulp is then sieved and stored in the form of a fine powder.

The Committee accepted the view of the applicant that this was a traditional foodstuff in Africa with evidence of safe consumption and, on this basis, the application could proceed without the provision of data from conventional toxicological analyses.

The Committee considered that the information provided regarding the presence of Ochratoxin A, a mycotoxin commonly associated with cereals, was of limited value. Given that, by the nature of the product there may be low levels of yeast and moulds present, Members requested reassurance that mycotoxins, which are commonly associated with dried fruit (e.g. aflatoxins), were not present in the baobab fruit products. Members also sought information regarding the harvesting, storage and transport procedures that would be employed and requested additional information in relation to the quality of the fruit as a result of early or late harvesting, and what would happen to damaged fruit.

Members considered the applicant's response at the March meeting and accepted information which showed the fruit pulp to have minimal contamination with soil and other detritus. The physical nature of the fruit (which resembles a coconut in hardness) provided some reassurance that damage leading to possible environmental and microbiological contamination would be minimal. Members also accepted additional information regarding the harvesting, storage and transport procedures that would be employed, noting that the applicant's quality assurance scheme included routine analysis for aflatoxins. However, Members sought clarification on discrepancies in the data sets describing the levels of acid insoluble ash and endogenous material derived from the fruit. The applicant's response allowed these remaining questions to be resolved at the July meeting.

The Committee's initial opinion was finalised and forwarded to the Commission for consideration by other Member States in July 2007. A copy of this opinion is attached as **Appendix V**.

1.5 Phosphated distarch phosphate

This application from National Starch was first described in the 2005 annual report. The Committee had previously requested additional information about potential gastrointestinal intolerance in high level consumers of the product. At the July meeting the Committee was asked to review the results of a new fermentability study. Members considered that it was not possible to extrapolate from the available data to the situation in young children, whose gut flora is developing and does not have an adult composition. It is known that children are more sensitive than adults to the laxative effects of other poorly absorbed ingredients e.g. polyols, and the Committee could not be certain that PDP will be tolerated to the same extent by children as by adults.

The Committee accepted additional information concerning the glycaemic response to PDP, but noted the possibility that insulin-dependent diabetics might suffer hypoglycaemia if their insulin dose was calculated on the basis of the glucose content of a meal that included the ingredient.

Members also expressed some concern regarding the proposed name for the ingredient, as there was already a legal name for the product when used as a food additive. At the November meeting the Committee agreed that the new proposed name for the ingredient "resistant (modified) (maize) starch" appeared to satisfy EU labelling requirements. With regard to potential intolerance in children, the Committee accepted the applicant's suggestion of advisory labelling but was of the view that this should not be restricted to children's food, and only apply to portions containing greater than 15g of the ingredient.

The Secretariat agreed to draft an opinion that reflected the Committee's discussions and this would be published for comment in early 2008.

1.6 Kiwiberry concentrate

This new application from Efficas, for a water extracted concentrate of dried hardy kiwi fruit *(Actinidia arguta)*, was first considered at the July meeting. Hardy kiwi is in the same genus as the familiar green kiwi *(Actinidia deliciosa)*, but is smaller with a fuzzless skin. The applicant proposed to market their kiwiberry concentrate, including a powdered form, for incorporation into a range of food products such as beverages, cereals and cereal products, milk and milk products, sugars, preserves and confectionary, and savoury snacks.

The Committee agreed that, based on the information provided by the applicant, there were no toxicity or nutritional concerns over this novel ingredient. However the Committee was concerned about the potential allergenicity of the product, given the close relationship between hardy kiwi and the conventional green kiwi, which is emerging as a significant food allergen in the UK and across Europe. The applicant had provided

data from an *in vitro* study which indicated that a small proportion of people with allergy to green kiwi may also react to the novel ingredient. However, this was a small study (12 subjects) and it was not possible to make a confident estimate of the true incidence of cross-reactivity.

Members were particularly concerned that the novel ingredient was proposed for use in a wide range of food products that would not be expected to contain kiwi fruit products. The existing allergenicity study had identified a single case of cross-reactivity, based on a screening test using serum from 12 individuals with existing kiwi fruit allergy. However, this test did not prove that individuals would actually cross-react to kiwiberry products on oral exposure. In these circumstances, the Committee advised that it would be inappropriate to apply a precautionary statement about kiwi allergy to the wide range of products in which the novel ingredient was to be used, as this would result in significant, and possibly unnecessary, restriction of choice. The Committee therefore indicated that additional studies should be carried out in order to determine the likely extent of the allergenicity.

The Committee considered this issue further at its meetings in September and November and confirmed that, in the absence of further data and in view of the potentially serious consequences of cross-reactivity in individuals previously sensitised to green kiwi fruit, it was not possible to conclude the risk assessment of this novel ingredient without further data. More specifically, data from *in vivo* studies were needed in order to determine the likelihood of allergic responses to the unprocessed kiwiberry fruit and to the heat-treated kiwiberry concentrate.

The consideration of this ingredient would continue once the applicant had provided its response to this request for further information.

1.7 Lycopene from *Blakeslea trispora*

This application from Vitatene for the use of a cold water dispersible preparation of lycopene, derived from the fungus *Blakeslea trispora*, was considered at the September meeting.

The Committee had delivered a positive opinion in 2004 on lycopene from *Blakeslea trispora* from the same manufacturer. An EU-wide authorisation was granted to the applicant in October 2006 covering a range of uses of their product, formulated in an oil suspension. This new application was essentially an extension of the use of the same ingredient, but in an alternative formulation that permitted its addition to a range of different foodstuffs where the oil suspension could not be used.

In the period since the original evaluation, two further novel food applications for the use of lycopene from other sources (a lycopene-rich oleoresin from tomatoes and a synthetic lycopene product) were under examination at EU level, following questions and concerns raised by some Member States.

Given that the European Food Safety Authority (EFSA) was also evaluating lycopene from all sources as part of a review of food colours, the Committee agreed that the novel food application should be referred to the European Commission for additional assessment, and an authorisation should be considered only when the EFSA review is completed.

In October, the Secretariat wrote to the European Commission indicating that the application should undergo an additional assessment **(Appendix VI)**.

1.8 beta-Glucan-rich extracts from *Lentinus edodes* (Shiitake mushroom extract)

This application from Glycanova (formally MediMush) was considered by the Committee at its November meeting. The Committee had previously rejected the same company's request for an opinion on substantial equivalence between this product and an existing beta-glucan product that is derived from a different part of the same mushroom species (see Item 2.4 below). The applicant therefore submitted a full application for authorisation of their mycelial extract as a novel food ingredient, for use in food supplements and a number of other food categories.

The Committee considered that the components present in the product had not been adequately characterised and requested further information. Evidence was also sought to support the statement that there was no effect of scale-up on the composition of the product, in order to confirm that data based on pilot scale fermentation systems could be used in the risk assessment. The Committee noted that the levels of lentinan, the primary beta-Glucan present in the product, were significantly lower than in Shiitake mushrooms themselves.

The Committee noted that the product caused inflammatory effects in animal studies, which would be expected for a beta-Glucan rich extract, and requested the original data sets to enable it to review these studies in detail.

The evaluation of this application would continue in 2008 once the applicant had responded to these points.

2 Substantial Equivalence Applications submitted to the UK Competent Authority

2.1 Astaxanthin: Cyanotech Corporation

This application from Cyanotech Corporation for an opinion on equivalence for their astaxanthin rich oleoresin, extracted from the alga *Haematococcus pluvialis*, was described in the 2006 Annual Report.

At its January meeting, the ACNFP concluded its assessment and agreed that the Cyanotech extract could be regarded as substantially equivalent to the existing *H. pluvialis* algal meal produced by Astacarotene. The Committee noted however that there appeared to be no routine scheme in place for the screening of cyanobacterial toxins and indicated that the applicant should ensure that such testing is carried out periodically to confirm the effectiveness of production controls. The Committee's opinion can be found in **Appendix VII**.

Cyanotech notified the European Commission of the placing on the market of their astaxanthin product on 7 March 2007.

2.2 Phytosterols: Lipofoods

An application was received from Lipofoods in November 2006 for a request for an opinion on substantial equivalence of their soyabean oil-derived phytosterols compared with phytosterols marketed by Archer Daniels Midland (ADM).

Lipofoods intended to use its ingredient in yellow fat spreads, salad dressing (including mayonnaise), milk type products such as semi skimmed and skimmed milk products, fermented milk products, such as yoghurt, soya drinks, and cheese. These products are the same as those authorised for ADM phytosterols.

The Committee had considered this request by postal consultation in November 2006. Members were content that these products could be considered substantially equivalent and did not request any further information. The Committee finalised its opinion in January 2007, indicating that substantial equivalence had been established between the products manufactured by Lipofoods and by ADM **(Appendix VIII)**.

Lipofoods notified the European Commission of the placing on the market of their phytosterol product on 16 Feb 2007.

2.3 Astaxanthin: Algatechnologies (1998) Ltd.

The ACNFP considered an application made by Algatechnologies (1998) Ltd., for an opinion on the equivalence of their astaxanthin-rich extract compared with an existing Astaxanthin-rich extract from the same source marketed by Valensa (formerly known as US Nutra). Both products are obtained from *H. pluvialis* algae using supercritical carbon dioxide extraction technology.

Valensa previously obtained a positive opinion from the ACNFP on the equivalence of their astaxanthin-rich extract with an existing algal meal (described in the 2004 Annual Report). Algatechnologies supplied Valensa with *H. pluvialis* meal as a raw material but now intend to manufacture their astaxanthin-rich oleoresin at a European plant using the same CO_2 technology and using the same source material.

Overall the Committee had no objections on this application but pointed out that the use of any additives, such as antioxidants, in the formulation of the product should comply with EU legislation.

However, during the 21 day public consultation of this application, comments were raised concerning the presence of a contaminant in the product and the absence of information regarding the stability of the product.

The consideration of this product was deferred to 2008, pending further information from the applicant on these issues.

2.4 beta-Glucan-rich extracts from *Lentinus edodes:* MediMush

The ACNFP considered an application made by MediMush AS for an opinion on substantial equivalence of a beta-Glucan-rich mycelial extract of *Lentinus edodes* (Shiitake mushroom) with an existing product namely the dried, pulverised fruiting bodies of *Lentinus edodes* marketed by Bio-Life Laboratorial Natural Products.

The Committee discussed this request on a number of occasions during 2007

The Committee accepted that it was reasonable, in principle, to compare the applicant's mycelial extract with the product that was already on the market, which is obtained from the dried fruiting bodies of the same species. However, the Committee advised that the initial application did not contain sufficient compositional and biochemical information to draw any conclusions. The Committee also sought further information regarding any other products on the market that were compositionally closer to the applicant's. The Committee noted advice from the Medicines and Healthcare products Regulatory Agency (MHRA) that the proposed uses of the product did not fall within the scope of medicines legislation.

The applicant supplied further information, which was considered by the Committee in March. The Committee requested more detailed information on the composition of the two products, as the available information was provided only in summary form and no statistical analysis had been carried out. The Committee also sought further evidence to support the argument that the same proteins are present in the mycelial extract and the fruiting bodies.

At the September meeting the Committee reviewed all the available information and concluded that, whilst there was a credible scientific rationale for equivalence of fungal mycelia to fruiting bodies, the compositional data provided by the applicant were insufficient and they had failed to demonstrate that the novel ingredient was substantially equivalent to its existing counterpart. This conclusion was set out in a letter to the applicant **(Appendix IX)**.

The applicant later provided a full novel food application for the same product (see Item 1.8 above).

2.5 Phytosterols: Naturis (ACI Group Ltd.)

At its November meeting, the ACNFP considered a request from the UK company Naturis for an opinion on equivalence of their phytosterols to be used in yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks and cheese type products with phytosterols marketed by Archer Daniels Midland (ADM)

ADM obtain their sterols from by-products of traditional vegetable oil refining. Their starting material is commonly a blend of crude edible oils, consisting largely of soy bean oil and lesser amounts of corn, rapeseed and palm oil. Naturis phytosterols are obtained from soya beans of non-GM origin, which fall within the range of source materials described by ADM.

The Committee noted that no information was provided on the production process used by the US manufacturer of the sterols and it was not possible, therefore, to determine the validity of the applicant's statement that the "process is very close to the one described in the SCF Opinion (reference 1) and ADM novel food application". Members also noted that the phytosterol ingredient contained 95% total sterols and asked for information on the composition of the remaining 5%.

The Secretariat agreed to obtain further information on these points. The Committee's consideration of this application would continue in 2008.

3 Applications submitted to other Member States

3.1 Synthetic Lycopene

At the January meeting, the Committee was asked to consider an initial opinion from the Dutch competent authority on an application from BASF for the authorisation of a synthetically produced lycopene product for use in a number of food categories and as a food supplement.

The Committee noted that the Joint FAO/WHO Expert Committee on Food Additives (JECFA) had recently assessed the safety of lycopene as a food colour and set an Acceptable Daily Intake of 0-0.5 mg/kg bw, a figure which was significantly lower than the estimated intake for this novel food ingredient. Members therefore suggested that the toxicological data used by JECFA to set an ADI for lycopene should also be taken into consideration in the assessment of this application (reference 2). The Committee also noted that the applicant specified that their ingredient contains 6-9% of related compounds (e.g. cis-isomers, rhodopin, acetyl-rhodopin), but that the test material used in the toxicological studies contained approximately 2% of related compounds. Members requested clarification of this discrepancy. The Committee's comments on this application were forwarded to the European Commission in January 2007 **(Appendix X)**.

3.2 Antarctic Krill Oil

In March 2007, the ACNFP considered a favourable opinion from the Finnish Competent Authority for authorisation of Antarctic krill oil as a novel food ingredient.

Krill oil is extracted from the crustacean *Euphasia superba*. The applicant intended to market this novel ingredient as a source of omega-3 fatty acids in a number of food categories including yoghurt, milk drinks, juices and protein bars, and as a food supplement.

Members were unable to agree with the positive opinion of the Finnish Competent Authority and highlighted a number of issues related to intake, labelling, allergy, Food Hygiene Regulations and the history of consumption of the source of the novel food. It was also noted that, although environmental factors are not among the criteria for acceptance of novel ingredients listed in Regulation (EC) 258/97, there was no information on the possible environmental impact on harvesting krill from the Antarctic region in order to produce the novel ingredient.

The Committee's comments on this application were forwarded to the European Commission in April 2007 **(Appendix XI)**.

The applicant produced an additional dossier to address the Committee's concerns, together with those raised by other Member States.

At its September meeting, the Committee confirmed it was content with the applicant's response to its concerns about intake levels, Food Hygiene Regulations, history of consumption and the environmental impact of fishing for krill.

The Committee reiterated its concerns about allergenicity, noting that the novel food ingredient had a high protein level compared with, for example, refined vegetable oils. The Committee therefore recommended that the novel ingredient should be labelled as not suitable for people with a shellfish allergy.

The Secretariat noted the Committee's comments, which will be used to inform the Food Standards Agency's position in future discussions on this novel ingredient, for example at meetings of the Standing Committee on the Food Chain and Animal Health.

3.3 Calcium L-methylfolate

In September 2007, the ACNFP considered an initial opinion from the Irish Competent Authority for the authorisation of calcium L-methylfolate as a novel food ingredient.

The calcium salt of L-5-methyltetrahydrofolic acid (5-MTHF) is intended for use as an alternative to folic acid. 5-MTHF is the predominant natural form of folate in many foods and it is also the form in which folate is stored in the human body and enters the circulation.

The safety and acceptability of this ingredient was already assessed by the European Food Safety Authority (EFSA) and Member States had agreed unanimously that it should be added to the list of permitted sources of folate in supplements and in foods for particular nutritional uses ("PARNUTS" foods). However, the use of this ingredient was subject to the Novel Food Regulation and therefore required to be authorised as a novel food ingredient before it could be used. In addition, the applicant proposed to add 5-MTHF to other foods that might be fortified with folate and also to infant formulae and follow-on milk.

The Committee agreed with the Irish initial assessment report that calcium L-methylfolate meets the criteria for acceptance as a novel food ingredient. However, Members noted that the use of this ingredient in infant formula was not covered by the existing risk assessments, and this use should only be authorised once it has been specifically evaluated by EFSA.

The Food Standards Agency wrote to the European Commission in October 2007 agreeing with the Irish initial assessment report on this application, with the proviso that use of this ingredient in infant formula and follow-on formula would require further assessment **(Appendix XII)**.

3.4 Noni Fruit Puree and Concentrate

In May 2007, the ACNFP considered a favourable initial opinion from the Belgian Competent Authority regarding an application submitted by Tahitian Noni International Inc, for authorisation of the use of noni fruit puree and concentrate as a novel ingredient in a number of food categories.

Members were unable to agree with the positive opinion of the Belgian Competent Authority and highlighted a number of issues relating to the projected intake of the ingredient.

It was noted that, by body weight, the highest consumers of the products for which the novel ingredients are intended will potentially be young children e.g. jellies, yoghurts and ice-cream. The Committee therefore considered that the risk assessment could not be completed without an estimate of the intake of the ingredients by children.

The information provided by the applicant regarding likely intake levels was based on US food consumption data and the Committee noted that this did not necessarily reflect consumption in the EU.

Members also pointed out that the EFSA Panel's recent conclusion that consumption of noni juice at the observed levels of consumption was unlikely to induce adverse effects on the liver, was based on the consumption of noni juice at the current observed levels of intake (reference 3). However, the noni fruit puree and concentrate will be available in a wide range of foods and this could result in considerably higher intake levels.

The Committee's comments on this application were forwarded to the European Commission in June 2007 **(Appendix XIII)**.

4 Notifications submitted to the European Commission

Under the novel food regulation authorisation applies to the applicant company only. However, where a novel food is "substantially equivalent" to a food already on the market, Regulation (EC) No 258/97 includes a provision for applicant companies to submit a notification to the European Commission after obtaining an opinion on equivalence from an EU Member State. According to Article 3(4) of Regulation (EC) No 258/97, that simplified procedure applies to foods or food ingredients that "are substantially equivalent to existing foods or food ingredients as regards their composition, nutritional value, metabolism, intended use and the level of undesirable substances contained therein".

During 2007 the Commission distributed a number of notifications for such products. As these notifications raised no new issues, they were brought to the Committee's attention but not discussed.

4.1 Noni juice

During 2007, the European Commission distributed a total of 7 notifications from companies for the marketing of noni juice that met the criteria for substantial equivalence with another noni juice product that is already on the EU market. These notifications are listed in Table 1 at **Appendix XIV**.

4.2 Phytosterols

As all phytosterol fortified products fall within the scope of the novel foods regulation, authorisations have been given to a number of companies for the use of plant sterols in a range of foods, including yellow fat spreads, milk type products, yoghurt type products, cheese type products, spicy sauces, soya drinks and salad dressings.

During 2007 the Commission distributed a total of 19 notifications from companies for the marketing of phytosterol fortified products that met the criteria for substantial equivalence. All the companies who have notified their products in the EU under this simplified procedure are listed in Table 2 at **Appendix XIV**.

4.3 Argan Oil

During 2007, the European Commission has distributed a total of 12 notifications from companies for the marketing of Argan oil that was judged to meet the criteria for substantial equivalence with vegetable oils (in particular peanut oil and sesame oil) already on the EU market. Table 3 at **Appendix XIV** lists these notifications.

5 Other issues considered by the ACNFP

5.1 Effects of GM Soya on newborn rats

In November 2005, the Committee issued a statement on research conducted by a Russian research team which had reported high levels of mortality in newborn rats fed with flour from GM (herbicide-resistant) soya beans. At that time, the Committee was unable to draw any conclusions from this research as the experimental conditions and the results were not available in sufficient detail and there were several possible explanations for the findings. The Committee agreed to reconsider the study if further information became available or if a fuller report was published in the scientific literature.

At the January 2007 meeting, the Committee noted that the researcher, Dr Irina Ermakova, had replied to the Committee and provided a list of additional publications. Dr Ermakova had also indicated that a paper containing information on pathological changes in the GM-soya fed rats was "in press". The Committee noted the reply from Dr Ermakova and advised that their original statement should remain as it still reflected their views. Members asked to see the paper on pathological changes once the peer-reviewed paper was published.

In November 2007 the Committee noted an article published in *Nature Biotechnology* (reference 4) on this research, in which Dr Ermakova stated that her research is being submitted for publication in the peer-reviewed literature. The Secretariat agreed to keep the Committee informed of any further developments.

5.2 Transformation-induced mutations in transgenic plants

At its March 2007 meeting, the Committee considered a recent, peer-reviewed review of mutations induced by GM transformation techniques (reference 5) and what implications this analysis had for the current approach to the risk assessment of foods derived from GM crops.

The Committee agreed that this was a useful review of the available literature and accepted that GM plants will contain unintended genetic changes. However, the Committee considered that this possibility was recognised and addressed in the current EU approach to the assessment of GM foods. The Committee noted that random genetic changes also occur in plants that have not undergone genetic modification and did not agree with the review authors' assumption that any unintended change to plant DNA equates to a risk to consumers.

The Secretariat's response to the authors of the paper can be found at **Appendix XV**.

5.3 Good Practice Guidelines for Scientific Committees

During 2007, the Food Standards Agency published Good Practice Guidelines for the operation of its various Scientific Committees, including the ACNFP. A copy of the Guidelines can be found at **Appendix I**.

It is intended that each Committee should review these guidelines on an annual basis. At its May 2007 meeting, the Committee considered whether any aspect of its operation should be revised in order to ensure a high level of compliance with the Guidelines. Members were satisfied that they adhered to the Guidelines and no revisions were suggested.

The Committee also noted that the Agency is exploring how it might improve the openness of Committee meetings. In the case of the ACNFP, restrictions associated with the EU authorisation procedures for novel and GM foods limit the ability to discuss current applications for authorisation in public. The Committee agreed however to hold an open meeting or workshop on general topics of interest to the public. This meeting was originally scheduled for November 2007 but was postponed to April 2008 for logistical reasons.

6 Developments elsewhere

6.1 Nutrition and Health Claims

The Committee received a presentation from the Food Standards Agency's Fortification and Claims Unit providing an overview of the legislation governing nutrition and health claims, which applies to all foods including novel foods.

Regulation (EC) 1924/2006 on nutrition and health claims came into force on 19 January 2007 and applies from 1 July 2007. The Agency expected that the enforcement measures would be in place in the autumn and would publish its final guidance to compliance as soon as possible.

The Agency was also assembling a national list of generally-accepted claims to be submitted for consideration by EFSA. A list of EU approved claims was expected to be in place by 2010. Until that time, claims would remain subject to general food labelling legislation that prohibits claims that are untrue or otherwise misleading to the consumer. Claims that state or imply that a food can prevent, treat or cure a disease will continue to be prohibited.

6.2 EFSA guidance and statements

Throughout the year, the Committee was updated on EC developments including the activities of the European Food Safety Authority (EFSA). In particular the Committee received information about the following EFSA publications:

- Statement on the safe use of the nptII antibiotic resistance marker gene in genetically modified plants by the Scientific Panel on genetically modified organisms (published in April 2007)

- Statement on the analysis of data from a 90-day rat feeding study with MON 863 maize by the Scientific Panel on genetically modified organisms (published in June 2007)

- Statement on the fate of recombinant DNA or proteins in the meat, milk or eggs of animals fed with GM feed (published in July 2007)

- Guidance document for the risk assessment of GM plants containing stacked transformation events (published in July 2007)

The Committee also received information about a special meeting of EFSA's Advisory Forum held in November 2007 to discuss GMO risk assessment, where the ACNFP Chairman had been part of the UK delegation. The Committee observed that the centralisation of risk assessments made it difficult for small companies to seek advice on their

applications prior to submitting them. Also, difficulties associated with travelling to Parma could discourage the best experts from participating in EFSA's Scientific Panels.

7 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:

ACNFP Secretariat
6th Floor
Aviation House
125 Kingsway
London
WC2B 6NH

Tel: 020 7276 8595
Fax: 020 7276 8564

The ACNFP website can be found at:
www.acnfp.gov.uk

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

8 References

1. Opinion of the Scientific Committee on Food on an application from ADM for approval of plant sterol-enriched foods (expressed on 4 April 2003).Available online at: http://www.efsa.europa.eu/food/fs/sc/scf/reports_en.html

2. Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessment on the safety of lycopene as a food colour. Available online at: http://www.fao.org/ag/agn/jecfa-additives/details.html?id=918

3. EFSA Opinion on a request from the Commission related to the safety on Noni juice (juice of the fruits of *Morinda citrifolia*). Available online at: http://www.efsa.europa.eu/it/science/nda_opinions/nda_op_ej376_noni.html

4. 'GM Soybeans and health safety – a controversy re examined' Andrew Marshall, *Nature Biotechnology* **25**; 981–987 (September 2007). Available online at: http://www.nature.com/nbt

5. Wilson *et al., Biotechnology and Genetic Engineering Review* **23**; 209–237 (2006).

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"

Officials of the Food Standards Agency provide the Secretariat. As well as formal meetings, the Committee organises workshops on specific topics related to its remit.

The interactions between the ACNFP and other independent advisory committees are outlined in Figure 1 (page 41).

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 2007, together with the names of the FSA 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 2007 can be found on page 24

A copy of the code of conduct for ACNFP members can be found on page 30.

Membership of the Committee during 2007

Chairman

Professor Mike Gasson BSc, PhD
Head of the Food Safety Science Division at the Institute of Food Research, Norwich.

Members

Professor Alan Malcolm MA, DPhil, FIFST, FIBiol,CBiol, FRSC (Nutritionist)
Chief Executive of the Institute of Biology.

Dr Anthony Williams BSc, MB, BS, DPhil, FRCP, FRCPCH (Paediatrician)
Consultant Neonatal Paediatrician and Senior Lecturer at St George's Hospital, Medical School, London.

Dr Claire Mills BSc, PhD (Plant science and allergy expert)
Head of the Structuring Food for Health Programme at the Institute of Food Research in Norwich.

Professor Gary Foster BSc, PhD (Molecular Biologist)
Professor in Molecular Plant Pathology in the School of Biological Sciences at the University of Bristol.

Professor Harry Flint BSc, PhD (Microbiologist)
Head of the Gut Microbiology and Immunology Division at the Rowett Research Institute.

Professor Ian Rowland BSc, PhD (Nutritionist/Toxicologist)
Professor of Human Nutrition at the University of Ulster and Head of the Northern Ireland Centre for Diet and Health.

Jayam Dalal (Consumer Representative)
Freelance marketing consultant.

Jill Brand MPhil, FICSc (Consumer Representative)
Home Economist.

Professor John Warner MB, ChB, MD, FRCP, FRCPCH Fmed, Sci (Allergenicity Expert)
Professor of Child Health at the University of Southampton and Head of the Department of Paediatrics at Imperial College.

Neville Craddock MA, CSci, FIFST (Food Processing and Quality Assurance Expert)
Independent food law consultant.

Dr Paul Brantom BSc, PhD, MIBiol (Toxicologist)
Independent consultant and registered European toxicologist.

Dr Peter Lund, BA, MA, DPhil (Molecular Biologist)
Senior lecturer in the School of Biosciences, University of Birmingham.

Professor Peter Shewry, BSc, PhD, DSc (Plant Biochemist)
Associate Director of Rothamsted Research.

Professor Ruth Chadwick BA, BPhil, DPhil (Ethicist)
Director of the ESRC Centre for Economic and Social Aspects of Genomics at Lancaster University.

Professor Stephen Holgate BSc, MBBS, MD, DSc, FRCP, FRCPath, FIBiol, FMed Sci (Allergenicity expert)
Medical Research Council Clinical Professor of Immunopharmacology at the University of Southampton.

FSA Assessors

Dr C Baynton	Food Standards Agency
Mr P Morgan	Food Standards Agency (Wales)
Ms E MacDonald	Food Standards Agency (Scotland)
Mr G McCurdy	Food Standards Agency (Northern Ireland)

ACNFP Members Interests during 2007

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
Professor M Gasson (Chairman)	Novacta Biosystems Ltd.	Shareholder.	Various.	IFR Food Safety Science Division industry-funded research projects.
Miss J Brand	None.	None.	None.	None.
Dr Paul Brantom	Perseus Ltd. Danisco Animal Nutrition. Elanco Animal Health.	Consultant.		
	Veterinary Products Committee (VPC). Veterinary Residues Committee (VRC). Advisory Committee on Animal Feedingstuffs (ACAF). EFSA Panel on Additives & Products or Substances used in Animal Feed (FEEDAP).	Committee Member.		

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor R Chadwick	Glaxo SmithKline.	Occasional consultant.	Food Ethics Council.	Member.
			ESRC. Wellcome Trust.	Research Funding.
			Eursafe.	Member of Executive Committee.
			Food & Agriculture Organisation Panel of Ethical Experts.	Member.
			MRC.	Steering Committee on DNA Banking.
Mr N Craddock	Various.	Consultant on short-term projects.	None.	None.
			Biohybrids.	Studentship.
Jayam Dalal	Agricultural Wages Committee.	Vice Chair.		
Professor Harry Flint	Shell.	Shareholder.	Provexis Alizyme.	Research funding.

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
Professor G Foster	BBSRC RAE Institute Assessment Exercise Science Panel.	Member.	BBSRC/DEFRA/ DfID/Gatsby. Horticultural Research International. Central Science Laboratories. British Society of Plant Pathology. Molecular Biotechnology. Glaxo SmithKline	Research Funding.
	BSPP/Blackwells Molecular Plant Pathology.	Editor-in-Chief.		
	Adjucation Panel for Science & Technology R&D funding in Ireland. Biotech/Molecular/ Biomedical Enterprise Ireland.	Panel Member.		
Professor S Holgate	Merck Research Laboratories. Novartis. Laboratorias Almirall. Pfizer. Altana Pharm. Centecor. Ferring. Wyeth. Amgen. Synairgen (Spin out company University of Southampton). Cambridge Antibody Technology. Kyowa Hakko. York Laboratories.	Consultant.	Novartis. MSD. Wyeth. Avantec.	Research Funding.

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
	Synairgen.	Shareholder/ Director.	Various charities and trusts.	Trustee.
	Southampton Asset Management.	Director.		
Dr P Lund	None.	None.	BBSRC. Leverhulme Trust. Darwin Trust.	Departmental Research.
			Food Ethics Council.	Director.
Professor A Malcolm	None.	None.	None.	None.
Dr Claire Mills	Standard Life.	Shares issued to Stakeholders when company sold.	Biochemical Society. FSA. IFRExtra. Various. Various.	Membership. Consultancy external reviewer of Food Allergy and Intolerance Research Programme. Analysis of Proteins in Oils. Starch work. Member of IFR Food and Health Network (Allergy cluster). EuroPrevall (EU funded) Industry partner.

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
Professor I Rowland	Alpro foundation. Glanbia. Clasado.	Consultant.	Vitacress. Geest. Cerestar (Belgium) Yakult UK.	Funded Research.
	Scientific Advisory Board of European Natural Soy foods Association (ENSA).	Member.		
	Halifax. Woolwich.	Shareholder.		
Professor P Shewry	Journal of Cereal.	Reviews editor.	Defra LINK programmes.	Funded Research.
	Various.	Occasional laboratory review panel member.	NIAB.	Trustee and Board Member.
	Various.	Editorial	Rank Prize Funds.	Trustee.
			Rank Prize Nutrition Committee.	Chair.

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor John Warner	UCB Pharma Ltd.	Chairman of Scientific Advisory Board.	Numico. UCB Pharma. Food & Drink Federation.	Funded Research.
	Merck.	Member of Scientific Advisory Board.	Anaphylaxis Campaign.	Trustee.
Dr A Williams	None.	None.	Rank Prize Funds. Children Nationwide.	Sponsorship of college course.
			National Childbirth Trust. La Léche League. Baby Milk Action. UK Association for Milk Banking. Breastfeeding Network. UNICEF (UK). Baby Friendly Initiative. Child Advocacy International. Nutricia. Interagency Group on Breastfeeding Monitoring.	Provision of un-paid advice.
			Women & Children First (charity organisation).	Trustee.

A CODE OF CONDUCT FOR MEMBERS OF THE ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES (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 the Board of the Food Standards Agency and Health Ministers, to Parliament and the public for its activities and for the standard of advice it provides.

The Board of the FSA and Health Ministers 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 33);

- 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 Food Standards Agency or Health Ministers;

- 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 Board of the Food Standards Agency 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 the Board of the FSA on any matter that 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 Board of the FSA, 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 the Board of the FSA 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 that may, or may be perceived (by a reasonable member of the public) to, influence their judgement. A guide to the types of interest that should be declared can be found on page 32 of this report.

(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 organisation and the nature of the interest are 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 members, 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.

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 that 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.

GOOD PRACTICE GUIDELINES FOR THE INDEPENDENT SCIENTIFIC ADVISORY COMMITTTEES

Preamble

Guidelines 2000: Scientific Advice and Policy Making[1] set out the basic principles which government departments should follow in assembling and using scientific advice, thus:

- think ahead, identifying the issues where scientific advice is needed at an early stage;
- get a wide range of advice from the best sources, particularly where there is scientific uncertainty; and
- publish the scientific advice they receive and all the relevant papers.

The C*ode of Practice for Scientific Advisory Committees*[2] (currently being updated) provided more detailed guidance specifically focused on the operation of scientific advisory committees (SACs). The Agency subsequently commissioned a *Report on the Review of Scientific Committees*[3] to ensure that the operation of its various advisory committees was consistent with the remit and values of the Agency, as well as the Code of Practice.

The Food Standards Agency's Board has adopted a **Science Checklist** (Board paper: FSA 06/02/07) to make explicit the points to be considered in the preparation of papers dealing with science-based issues which are either assembled by the Executive or which draw on advice from the Scientific Advisory Committees.

The Board welcomed a proposal from the Chairs of the independent SACs to draw up **Good Practice Guidelines** based on, and complementing, the **Science Checklist**.

[1] Guidelines on Scientific Analysis in Policy Making, OST, October 2005. Guidelines 2000: Scientific advice and policy-making. OST July 2000

[2] Code of Practice for Scientific Advisory Committees, OST December 2001

[3] Report on the Review of Scientific Committees, FSA, March 2002

The Good Practice Guidelines

These Guidelines have been developed by 9 advisory committees:

Advisory Committee on Animal Feedingstuffs[4]
Advisory Committee on Microbiological Safety of Foods
Advisory Committee on Novel Foods and Processes
Advisory Committee on Research
Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment[5]
Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment[6]
Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment[7]
Scientific Advisory Committee on Nutrition[8]
Spongiform Encephalopathy Advisory Committee[9]

These committees share important characteristics. They:

- are independent;
- work in an open and transparent way; and
- are concerned with risk assessment not risk management.

The Guidelines relate primarily to the risk assessment process since this is the committees' purpose. However, the Agency may wish on occasion to ask the independent scientific advisory committees whether a particular risk management option is consistent with their risk assessment.

Twenty eight principles of good practice have been developed. However, the different committees have different duties and discharge those duties in different ways. Therefore, not all of the principles set out below will be applicable to all of the committees, all of the time.

This list of principles will be reconsidered by each committee annually as part of the preparation of its Annual report, and will be attached as an Annex to it.

[4] Joint FSA/Defra Secretariat, FSA lead
[5] Joint FSA/HPA Secretariat, HPA lead
[6] Joint FSA/HPA Secretariat, HPA lead
[7] Joint FSA/HPA, FSA lead
[8] Joint FSA/DH Secretariat
[9] Joint Defra/FSA/DH Secretariat

Principles

Defining the issue

1. The FSA will ensure that the issue to be addressed is clearly defined and takes account of stakeholder expectations. The committee Chair will refer back to the Agency if discussion suggests that a re-definition is necessary.

Seeking input

2. The Secretariat will ensure that stakeholders are consulted at appropriate points in the committee's considerations and, wherever possible, SAC discussions should be held in public.

3. The scope of literature searches made on behalf of the committee will be clearly set out.

4. Steps will be taken to ensure that all available and relevant scientific evidence is rigorously considered by the committee, including consulting external/additional scientific experts who may know of relevant unpublished or pre-publication data.

5. Data from stakeholders will be considered and weighted according to quality by the committee.

6. Consideration by the secretariat and the Chair will be given to whether expertise in other disciplines will be needed.

7. Consideration will be given by the Secretariat or by the committee to whether other scientific advisory committees need to be consulted.

Validation

8. Study design, methods of measurement and the way that analysis of data has been carried out will be assessed by the committee.

9. If qualitative data have been used, they will be assessed by the committee in accordance with the principles of good practice, e.g. set out in guidance from the Government's Chief Social Researcher[10].

10. Formal statistical analyses will be included wherever possible. To support this, each committee will have access to advice on quantitative analysis and modelling as needed.

[10] There is of guidance issued under the auspices of the Government's Social Research Unit and the Chief Social Researcher's Office (Quality in Qualitative Evaluation: A Framework for assessing research evidence. August 2003. www.strategy.gov.uk/downloads/su/qual/downloads/qqe-rep.pdf and The Magenta Book. www.gsr.gov.uk/professional_guidance/magenta_book/guidance.asp).

11. When considering what evidence needs to be collected for assessment, the following points will be considered:

    - the potential for the need for different data for different parts of the UK or the relevance to the UK situation for any data originating outside the UK; and

    - whether stakeholders can provide unpublished data.

12. The list of references will make it clear which references have either not been subject to peer review or where evaluation by the committee itself has conducted the peer review.

Uncertainty

13. When reporting outcomes, committees will make explicit the level and type of uncertainty (both limitations on the quality of the available data and lack of knowledge) associated with their advice.

14. Any assumptions made by the committee will be clearly spelled out, and, in reviews, previous assumptions will be challenged.

15. Data gaps will be identified and their impact on uncertainty assessed by the committee.

16. An indication will be given by the committee about whether the database is changing or static.

Drawing conclusions

17. The committee will be broad-minded, acknowledging where conflicting views exist and considering whether alternative hypotheses fit the same evidence.

18. Where both risks and benefits have been considered, the committee will address each with the same rigour.

19. Committee decisions will include an explanation of where differences of opinion have arisen during discussions, specifically where there are unresolved issues and why conclusions have been reached.

20. The committee's interpretation of results, recommended actions or advice will be consistent with the quantitative and/or qualitative evidence and the degree of uncertainty associated with it.

21. Committees will make recommendations about general issues that may have relevance for other committees.

Communicating committees' conclusions

22. Conclusions will be expressed by the committee in clear, simple terms and use the minimum caveats consistent with accuracy.

23. It will be made clear by the committee where assessments have been based on the work of other bodies and where the committee has started afresh, and there will be a clear statement of how the current conclusions compare with previous assessments.

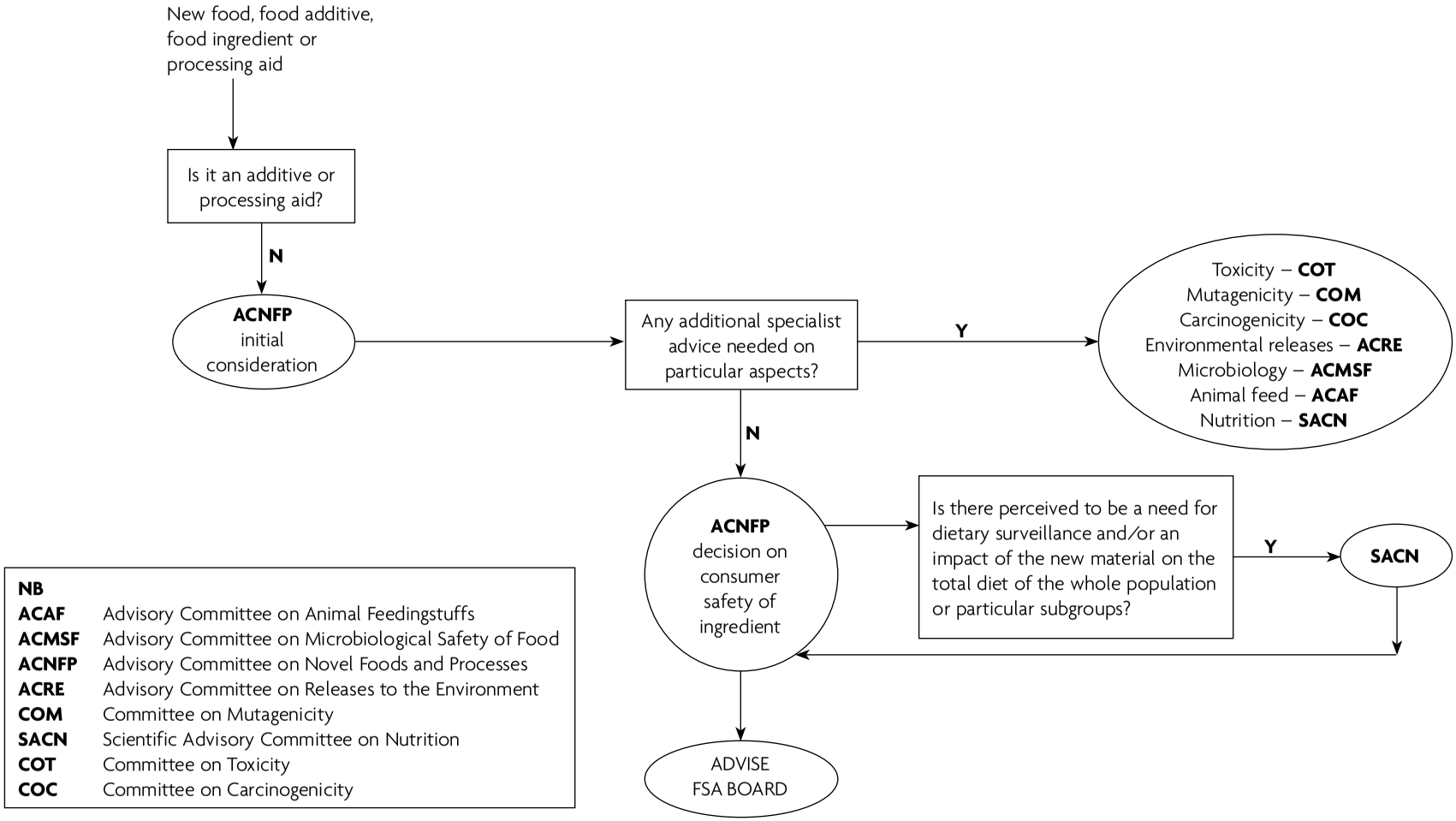
24. The conclusions will be supported by a statement about their robustness and the extent to which judgement has had to be used.

25. As standard practice, the committee secretariat will publish a full set of references (including the data used as the basis for risk assessment and other committee opinions) at as early a stage as possible to support openness and transparency of decision-making. Where this is not possible, reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

26. The amount of material withheld by the committee or FSA as being confidential will be kept to a minimum. Where it is not possible to release material, the reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

27. Where proposals or papers being considered by the Board rest on scientific evidence, the Chair of the relevant scientific advisory committee (or a nominated expert member) will be invited to the table at Open Board meetings to provide this assurance and to answer Members' questions on the science. To maintain appropriate separation of risk assessment and risk management processes, the role of the Chairs will be limited to providing an independent view on how their committee's advice has been reflected in the relevant policy proposals. The Chairs may also, where appropriate, be invited to provide factual briefing to Board members about particular issues within their committees' remits, in advance of discussion at open Board meetings.

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



APPENDIX II

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Initial opinion on an application under the novel foods Regulation for refined Echium Oil derived from *Echium plantagineum* as a food ingredient

Applicant: Croda Chemicals Europe Ltd.

Responsible Person: David Parker

EC Classification: 2.2

Introduction

1. An application was submitted to the Food Standards Agency in August 2006 by Croda Chemicals Europe Ltd. for the authorisation of refined echium oil as a novel food ingredient. A copy of the application was placed on the Agency's website for public consultation.

2. Echium oil is a vegetable oil rich in omega-6 and omega-3 polyunsaturated fatty acids and is obtained by refining oil extracted from the seeds of *Echium plantagineum*, which is a member of the *Boraginaceae* family. The applicant proposes to market their refined echium oil as a novel food ingredient in a range of food products (including milk and yoghurt-based drinks, breakfast cereals and nutrition bars) and in food supplements.

3. The application for authorisation of refined echium oil was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. The applicant's refined echium oil has been classified as a complex novel food from non-GM sources (class 2.2).

I. Specification of the novel food

Information on this aspect is provided on p. 3-12 of the application dossier

4. The novel ingredient (NI) is obtained from the seeds of *Echium plantagineum* using a solvent chromatographic technique and is rich in stearidonic acid (STA; cis-6, 9, 12, 15-octadecatetraenoic acid).

5. The NI is a pale yellow fully refined oil and the applicant has provided the following proposed specification:

Stearidonic acid content	Not less than 10% w/w of total fatty acids
Trans fatty acids	not more than 2% w/w of total fatty acids
Unsaponifable content	not more than 2%
Acid value	not more than 5mg KOH/g
Peroxide value	not more than 5 meq O_2/kg
Lead	not more than 0.1 mg/kg
Protein content (total nitrogen)	not more than 20 μg/ml

6. Compositional data were provided on three batches of the NI, the raw material and a blend of the NI which confirmed that the NI is produced consistently to meet the above specification.

7. The applicant has quality control procedures in place to ensure that that the NI meets the stated specification. If the NI does not meet this specification it will not be released. The applicant has stated that the standard site procedures for reprocessing are;

   - If the material failure is considered marginal, for example in terms of colour, then it is reprocessed. The material is either re-refined or blended with another batch of material and then re-refined to generate a product that is in specification.

   - If the failure of specification is significant, and it is not possible to remedy by reprocessing, the material will be discarded.

8. Unsaponifiable matter from both the raw material and three production batches of the NI was investigated using GC analysis which demonstrated that the NI contains between 0.80 and 0.87% (1.08% in the crude oil). Independent analysis has confirmed that the trans fatty acid content is below 2g/100g oil (% w/w).

9. The applicant also provided details on the sterol content of the NI, which was compared with traditional counterparts such as borage, blackcurrant, evening primrose and safflower. The applicant was therefore, of the view that this demonstrated that the sterol profile of the NI is within the range of other commonly consumed oil. For example, the levels of campesterol in the NI ranged from 23-28% compared to 25-30% in borage oil.

10. Approved agrochemical products could potentially be used at the production cycle of *Echium plantagineum* for weed control or as a pre-harvest desiccant. Analysis confirmed that no residues of pesticides are detectable in the NI.

11. Analysis of both the crude oil and the NI confirms that heavy metals such as arsenic and cadmium are all below detection limits. The NI complies with EU contaminants legislation, which specifies an upper limit of 0.1mg/kg for lead in vegetable oil. Analytical data have been provided to demonstrate that the levels of dioxins, furans, dioxin-like PCB's and PAH's are all below the maximum permitted levels (Annex A appendix 1, parts G and H).

12. The NI is stabilised with approved antioxidants, which have been added in accordance with Directive 95/2/EC on food additives other than colours and sweeteners. The applicant has measured oxidation of the oil using the peroxide value (PV) and the p-anisidine value (p-AV), which are measures of the extent of oxidation in materials containing unsaturated fatty acids such as the NI and ensures that it is produced to a set specification.

13. In addition the applicant tested the oxidative stability of the NI using an automated test system (Rancimat) and compared the results with traditional counterparts. The NI was studied under identical conditions to other vegetable derived oils with the exception of a higher temperature. The reaction kinetics for oxidation indicated that an induction time in the region of 2.5 hours would be obtained at 100^0C, which would be comparable to other oils.

Discussion: *The Committee noted the applicant's proposed specification for the NI.*

II. Effect of the production process applied to the novel food

Information on this aspect is provided on p. 14-17 of the application dossier

14. The *E. plantagineum* crop used to produce the NI is to be grown under contract in the UK. The production process is patented and involves cracking the echium seeds and extraction using hexane, followed by a series of distillation and filtration steps. The residual level of hexane in the oil is less then 1mg/kg, consistent with the requirements of EC legislation on extraction solvents (Directive 88/388/EEC).

15. The NI is processed in a batch-wise manner using a commercial scale chromatographic technique developed by the applicant to achieve high purity natural oils.

16. The production process of the NI has been independently assessed and certified in accordance with HACCP, which is in place throughout the production process.

    Discussion: *The Committee was satisfied that the applicant's proposed production process for the NI did not give cause for concern.*

III. History of the organism used as a source of the novel food

Information on this aspect is provided on p.18-20 of the application dossier

17. The NI is derived from the seeds of *E. plantagineum*, which is a member of the *Boraginacea* family. The *Boraginacea* family is a large plant family with approximately 100 genera and 2,500 species, which are widely distributed and well known to herbalists.

18. *E.plantagineum* is also known by its common names of Purple Vipers Bugloss, Paterson's Curse and Salvation Jane. It is an erect, biennial, soft hairy plant with one or many flowering stems. *E. plantagineum* is widespread throughout Australia and is eaten readily by livestock.

    Discussion: *The Committee noted that current consumption of E. plantagineum as a food is very limited.*

IX. Anticipated intake/extent of use of the novel food

Information on this aspect is provided on p.23-28 of the application dossier

19. The applicant intends that the NI will be used as an ingredient in a variety of products.

20. A complete list of products and levels at which refined echium oil will be added (expressed in terms of Stearidonic acid (STA), which comprises not less than 10% of the oil) can be found below. According to the applicant these use levels are largely based on the delivery of approximately 200mg of STA per day. The products will not be restricted locally and there are no plans to target a particular consumer group. However, the applicant anticipates that products containing the NI will be primarily consumed by vegetarians as an alternative to flax oil, borage oil and other existing sources of omega-3 fatty acids.

Summary of the proposed food uses and use levels (expressed as STA) for Refined Echium Oil		
Food Category	**Food use**	**Maximum Use Level (mg STA/100g)**
Dairy products	Milk	75
	Cheese	250
	Fromage frais	250
	Yoghurt	75
Dairy analogues	Soy products	250 750 in cheese analogues
	Imitation milk products	250
Fats and dressings	Spreadable fats and dressings	750
Grain based products	Breakfast cereals	625
	Nutrition bars	500
	Bread products	200
Meal replacements	Meal replacement beverages	250
Sauces	Savoury sauces	500 (200 in pasta sauces)
Fruit juice products	Fruit juices	75
	Fruit smoothies	75
	Ready-to-drink soft drinks (not low calorie)	75
	Ready-to-drink soft drinks (low calorie)	75
Dietary foods for special medical purposes		In accordance with the particular nutritional requirements of the persons for whom products are intended
Food supplements		500 (mg STA per daily dose as recommended by the manufacture)

21. Based on these proposed use levels the applicant has estimated the daily intake of STA using the data from the National Dietary Nutrition Survey (NDNS) of 1992/3 for children aged 1.5-4.5, 1997 for young people aged 4-18 and 2000/1 for adults aged 18-64. A summary of the estimated intake for different age groups can be found below:

From Table IX.a-2 Summary of the Estimated Daily Intake of STA from Refined Echium Oil from All Proposed Food Categories in the U.K. by Population Group (NDNS Data)							
Population Group	Age (Years)	% Users	Actual # of Total Users	All-Person Consumption (mg/day)			
				Mean	Percentile		
					90	95	97.5
Children	1½ to 4½	98.8	1628	719	1053	1216	1354
Young People	4 to 10	99.6	834	860	1234	1371	1561
Female Teenagers	11 to 18	97.8	436	805	1265	1403	1594
Male Teenagers	11 to 18	99.5	414	1056	1647	18723	2076
Female Adults	16 to 64	94.3	903	866	1325	1507	1692
Male Adults	16 to 64	95.0	728	1124	1751	19312	2189

22. The applicant's estimates of mean daily intake vary between 719 mg/person for children to 1124 mg/person for male adults and the high level daily intake (97.5th centile) varies between 1354 mg/person for children and 2189 mg/person for male adults. The applicant has explained that the highest level exposure to the NI (the 97.5th percentile of estimated intake in male adults) is equivalent to 11 servings of foods containing the NI, or approximately 2200 mg of STA. In practice this is an over-estimate and it is unlikely that these "worst case" intake levels will be achieved in practice as it is extremely unlikely that consumers will choose so many products containing the NI. (see paragraph 42 below)

23. The applicant was also asked to provide information on the EDI of the echium oil itself. (Note: the following estimates are based on consumers of the fortified products rather than the whole population, i.e. "users only" rather than "all person").The applicant reported that the greatest mean and 97.5th percentile intakes of echium oil (on an absolute basis) are found in male adults, at approximately 9g and 17g person/day, respectively. On a body-weight basis, children were identified as having the highest intakes of any population group, with mean and 97.5th percentile all-user echium oil intakes of 0.4 and 0.8 g/kg body weight/day respectively.

Discussion: *The Committee considered that the consumption of the NI at the proposed levels of incorporation in the different food categories did not raise any specific safety concerns.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p.29-33 of the application dossier

24. The NI contains fatty acids commonly found in the diet such as 6% palmitic acid, 3.5% stearic acid, 17.2% oleic acid, 18.6% linoleic acid, 29.5% alpha linoleic acid, 10.2% gamma linoleic acid and 12.6% stearidonic acid.

25. From a nutritional safety perspective the applicant considers that the NI is equivalent to existing oils and fats that are rich in essential fatty acids.

26. The applicant notes that animal and human studies have demonstrated that STA can be efficiently converted into eicosapentaenoic acid (EPA). EPA displaces arachidonic acid in platelet membranes, which results in an alteration in eicosanoid production in favour of platelet anti-aggregatory mediators. A combined daily intake of EPA and DHA in excess of 3g/day has been associated with a reduction in platelet aggregation and an increase in bleeding time and for this reason subjects receiving anti-coagulant therapy should avoid consuming foods rich in EPA and DHA. The applicant notes that the intake of refined echium oil may result in a decrease in triglyceride levels in healthy subjects with normal or low triglyceride levels. These effects have typically not been considered with other nutritional products known to reduce triglyceride levels (i.e. soy, fish oil and certain fibres).

27. In response to a request from the Committee, the applicant has explained that the maximum amount of EPA that might be theoretically produced from ALA and STA in the echium oil, even in high level consumers, is well below the 3 g/day threshold of EPA and DHA that has been set by other regulatory bodies for the prevention of changes to platelet function and bleeding time, and well below the amounts administered in studies assessing the effects of combined administration of anticoagulants and EPA/DHA. The applicant was of the view that at the proposed levels of use, the NI is not expected to increase the risk of bleeding in individuals receiving anticoagulant therapy.

28. In its initial discussions, the Committee was concerned that the NI could be seen as an alternative to other sources of polyunsaturated fatty acids, although the nutritional value of STA is lower than that of other PUFAs such are EHA and DPA. Consumers might therefore be disadvantaged if they consumed products containing the NI in preference to products such as oily fish, for which a nutritional benefit has been established. The applicant explained that it proposes to label the NI as "refined echium (vegetable) oil". This, in the view of the applicant should distinguish it from fish oils which are the predominant source of DHA/EPA in the diet and are focussed on cardiovascular health. The applicant also stressed that echium oil is

rich in the essential fatty acids alpha-linolenic acid (ALA, Omega-3) and d-gamma-linolenic acid (GLA, Omega-6) which are precursors for eicosanoids in the body. The applicant highlights that ALA is recognised as being of nutritional importance in its own right, and a number of Member States have set a daily recommended value of up to 2.2 g per day for total omega-3 fatty acids. The applicant also pointed out that a similar product, flax seed oil (linseed) oil, is widely available on the market and is included in many food supplements, including combinations with fish oils. The applicant stated that the NI would be an alternative vegetable based source of essential omega-3 and omega-6 fatty acids, similar to flaxseed oil.

Discussion: *The Committee was satisfied with the nutritional information provided for the NI and was content that the NI would not be nutritionally disadvantageous to consumers. Members also agreed that the product would be marketed in the same market sector as existing vegetable oils and would not be viewed as an alternative to fish oils.*

XII. Microbiological information on the novel food

Information on this aspect is provided on p.34-35 of the application dossier

29. The NI is produced in an anhydrous system and will therefore not support microbial growth. Also the production of the NI includes a range of chromatographic techniques which work to filter any microbial organisms and the production is controlled through HACCP procedures.

30. In response to a request by the ACNFP the applicant confirmed that the HACCP certificate provided in the application, which was for the manufacture of fish oil concentrates and refined vegetable oil for use in animal feeds, is also applicable for food grade oil.

31. Microbiological analyses on the NI demonstrated the absence of microbiological contamination and are summarised below;

    - Osmophilic yeast <10cfu/g
    - Yeast <10cfu/g
    - Moulds <10cfu/g
    - Enterobacteria <10cfu/g
    - *Staphylococcus aureus* <10cfu/g

Discussion: *The Committee was of the view that the microbiological safety of the NI had been demonstrated and noted that the manufacturer's HACCP procedures are also applicable for food grade oil.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 4-5 and p.26-46

32. Pyrrolizidine alkaloids and cytochrome C allergens are two known potentially toxic inherent constituents that are associated with the *Boraginacea* family.

33. The applicant does not anticipate that pyrrolizidine alkaloids (PA) will be present in the NI due to the fact that they are polar compounds and not expected to be carried over into the hexane-extracted oil and subsequently refined. The applicant has carried out analysis to confirm that PA levels are below the limit of detection (limit of detection = 4μg PA/kg oil).

34. Cytochrome C allergens have been characterised as proteins with a molecular weight of 12,800 and the applicant notes that the chromatographic technique used to refine the NI will act to remove any pollen or particulate plant debris in the oil. The applicant analysed both the NI and the crude oil for protein content using the Bradford assay. The protein content of the crude oil was 210μg/ml whilst the NI contained less than the limit of detection of 10μg/ml. The proposed specification for the NI allows a maximum protein content of 20μg/ml.

35. Echium has been extensively studied at both the whole plant and extracted oil levels. The applicant has identified that the critical risk factors pyrrolizidine alkoloid and cytochrome C are effectively absent in the NI. Using the data from paragraph 11, the maximum possible intake of PA would be less than 0.1 μg/day, assuming the "worst case" intake of 20g of the NI containing 4 μg of PA per kg. This is considerably lower than the doses of PA associated with toxicity (70-147 mg/day for infants and 570-1380 mg/day for adults).

36. Echium has also been associated with respiratory allergy (cytochrome C allergens) in the pollen of the plant. The protein content of the oil is reported to be <10μg/ml in all 3 batches tested (see paragraph 34 above). Assuming the worst case, i.e. that the oil contains 10μg/ml protein and that 100% of that protein is cytochrome C allergens, then the consumption of 20g of the oil would result in the intake of 200μg of allergenic protein. The applicant suggested that this is below what would be required to trigger an allergic reaction in a sensitive individual and, furthermore, it is likely that heat treatments during the manufacturing process will denature the protein so reducing its allergenicity.

37. The Committee accepted that it was very unlikely that serious allergic reaction, such as anaphylaxis, would result from the intake of this small amount of allergenic protein. The Committee nevertheless asked the applicant to provide further details of the protein composition to confirm that the cytochrome C allergen is not

actually present at the level suggested by this worst case analysis. The protein was extracted from both crude and refined echium oil using a modified Olszewski *et al*. procedure where the crude oil was shown to contain 21.2μg protein/g and the refined oil contained 11.1μg protein/g. Analysis of the limit of detection for cytochrome C by gel electrophoresis and of the recovery from the extraction procedure led to the conclusion that the refined oil contained less than 3μg cytochrome C per kg of oil.

38. The metabolism of STA and STA-rich oil has also been studied to determine whether consumption of STA increases EPA levels in the bloodstream.

39. The applicant has detailed a series of feeding studies on both the echuim oil itself and on stearidonic acid. The applicant has provided a summary of the oil profiles and dose levels of the echium oil used in these studies, and these are presented in the following table:

Study		Dose level	Results
Toxicology studies on Echium oil			
4 week dietary exposure in rats		Diets containing 5% sunflower, flaxseed, echium (containing 12.5% STA) and canola oils	• No significant difference in body weight • Echium oil may be useful for elevating EPA and DPA n-3 in the body.
12 week clinical study – Healthy young males	Part 1: Immune Function	9g of echium oil per day containing 1g of STA	• No effect on immune function at 1g/day
	Part 2: Fatty acid composition in blood lipids and mononuclear cells	9g per day of 1 of the 7 oil blends. (Each oil blend consisted of palm oil, sunflower oil, EPA rich oil, borage oil and echium oil at various levels)	• No significant effects were observed with each lipid fraction • STA may be used as a precursor to increase the EPA content of human lipids
4 week clinical trial in asymptomatic subjects with mild to moderate hypertriglyceridemia		Subjects followed the US National Cholesterol Education Programme Step 1 – 15 g echium oil [supplied by the applicant] (containing approx. 1.9 of STA) per day	• No significant differences between baseline values of vital signs and clinical laboratory markers. • Dietary plant oils rich in STA are metabolised to longer chain, more unsaturated (n-3) PUFA • Oils appear to posses hypotriglyceridemic properties which are usually associated with fish oil

Study	Dose level	Results
Toxicology studies on stearidonic acid		
In vitro study – Modification of liver fatty acid metabolism in mice by n-3 and n-6 delta 6-desaturase substrates and products	Mice fed a fat free semi-purified diet supplemented with 1% (w/w) fatty acid ethyl ester mixture	• Competition for subsequent metabolic enzymes • n-6 fatty acids derived from GLA are incorporated more favourably into liver phospholipids.
In vivo – comparison of the conversion rates of ALA and STA to longer polyunsaturated fatty acids in rats	Lipid free diet supplemented with lard (9% w/w) and either ALA ethyl esters (1%) or STA ethyl esters (1%)	• STA found in liver lipid fraction in small amounts. • Desaturation at C-6 is the rate limiting step in the conversion of ALA to EPA
3 week dietary exposure in rats	TAG mixtures containing 10% of STA, ALA or EPA	• No differences in n-3 PUFA's were observed
7 week dietary exposure in mice	Ethyl esters of ALA, STA, EPA, DHA, CLA and GLA compared with oleic acid at a level of 3g/100g in the diets of APC.	• No significant difference between prostaglandin levels or body weight • STA and EPA attenuate tumorigenesis and this effect may be related in part to alterations in prostaglandin biosynthesis
3 week clinical study in humans	Encapsulated STA, ALA or EPA ingested in daily does of 0.75g and then 1.5g	• No consistent effect on lipopolysaccharide stimulated synthesis of prostaglandin E2 and thromboxane A2 • No significant differences between groups

40. The applicant has concluded that refined echium oil is comparable in most respects to other plant oils used as foods but it contains a higher level of STA.

41. The applicant notes that none of the toxicity studies allow the setting of a No Observed Adverse Effect Level. However from a human nutritional safety perspective the applicant considers that the two most important clinical studies are those in which echium oil was consumed at levels resulting in up to 1.9g STA per day and for periods for up to 12 weeks. In these studies echium oil was found to have no significant effect on immune function, to decrease serum triglycerides and to have no effect on cholesterol.

42. In light of the information from these studies the applicant considers that 1.9g/person/day is a safe intake level of STA in humans, when consumed in the form of refined echium oil. Therefore, the proposed maximum use level of 200mg of STA per daily serving of various foods would allow for consumption of approximately 9-10 daily servings. (See paragraph 22).

    Discussion: *The Committee queried the level of protein present in the NI and requested additional information. Members reviewed the results of the additional studies carried out by applicant and were content that these provided the necessary reassurance there were no significant levels of protein present. The Committee also confirmed that they were content with the toxicological assessment carried out by the applicant on the NI which showed it is safe for human consumption at the proposed level of use.*

Labelling

Information on this aspect is provided on p.i of the application dossier

43. Although the applicant initially proposed to describe the NI as STA (stearidonic acid)-rich oil *from *Echium plantagineum*" (where * may be used as a footnote), the Committee was of the view that the average consumer may not understand what STA is. The applicant therefore proposed that at a minimum the term "refined echium (vegetable) oil", will be included on the ingredient list of the final food and that, in addition to normal fat labelling requirements, the stearidonic acid content and total omega-3 fatty acid content will be included in the nutrition panel of the food.

    Discussion: *The Committee was content with the applicants proposed labelling of food products containing the NI and noted that any labelling concerning the nutrient content of foods containing the novel ingredient must comply with the relevant legislation.*

Conclusion

44. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by Croda Chemicals Europe Ltd that the range of uses for its refined echium oil is acceptable, subject to the applicant's adherence to the proposed specification and the production parameters described above. The Committee also wishes to note that any foods containing this novel ingredient should be labelled in accordance with existing legislation and should not make claims that are likely to mislead consumer.

July 2007

APPENDIX III

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on an application under the novel foods Regulation for ice structuring protein preparation derived from fermented genetically modified baker's yeast *Saccharomyces cerevisiae* as a food ingredient

Applicant: Unilever PLC

Responsible Person: Dr George Gordon

EC Classification: 5.1

Introduction

1. An application was submitted by Unilever PLC on 15 June 2006 for the authorisation of an ice structuring protein Type III HPLC 12 preparation derived from a fermented genetically modified baker's yeast as a novel food ingredient. A copy of the application dossier was placed on the FSA website for public consultation.

2. Ice structuring proteins (ISP) are naturally occurring proteins and peptides, which are found in a variety of living organisms such as fish. ISP protect them from damage to tissues in very cold conditions by lowering the temperature at which ice crystals grow and by modifying the size and shape of ice crystals. ISP found in ocean pout[11] are defined as Type I, II, III or IV. Twelve different ISP type III have been identified in the serum of ocean pout using high performance liquid chromatography (ISP Type III HPLC 1-12).

3. The applicant states that sourcing ISP Type III from ocean pout is not sustainable or economically feasible. The applicant has therefore developed a fermentation system using a genetically modified baker's yeast (*Saccharomyces cerevisiae*) carrying a synthetic gene encoding for the ISP Type III HPLC 12.

4. Unilever seeks approval to market its ISP Type III HPLC 12 preparation in edible ices at level not exceeding 0.2%. The presence of the ISP Type III HPLC 12 during the manufacture of frozen products, at the freezing stage, causes ice crystals to form in a particular way so that there are a large number of very small crystals. Normally, in these products, there are a small number of relatively large ice crystals. The continuing presence of the ISP is not necessary for the maintenance

[11] Cold water fish found off the North East American coast (*Macrozoarces americanus*)

of the small crystal size once the product is frozen. Physical interactions between the very small ice crystals provide a structure that differs from conventionally frozen iced products. This effect allows, for example, the production of ice cream with a low fat content.

5. The applicant's ISP Type III HPLC 12 preparation has already been authorised in Australia, New Zealand, Chile, Indonesia, Mexico, the United States and the Philippines under their local regulatory procedures[12]. In the EU, ingredients produced by fermentation using genetically modified micro-organisms, not present in the final product, do not fall under the scope of the regulation 1829/2003 on GM food and feed[13], and this therefore applies to Unilever's ISP preparation as the yeast cells are removed from the final product. In the EU, the proposed ISP Type III HPLC 12 preparation is considered to be a novel food ingredient as it has no significant history of consumption in the EU prior to 15 May 1997. It therefore falls under the scope of the novel food regulation (EC) 258/97 (Article 1(2)(d)). This was confirmed at the Standing Committee on Food Chain and Animal Health meeting of 14 December 2006[14], which concluded that the ISP preparation should be regarded as a novel ingredient and not as a food additive.

6. The application for authorisation of this preparation was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. This preparation has been classified as a product of a GM microorganism, the host microorganism used for the genetic modification having a history of use as food or as a source of food in the Community under comparable conditions of preparation and intake (class 5.1).

7. EFSA have recently published their guidance document on the risk assessment of products derived from genetically modified microorganisms[15] (GMMs). The scope of this document includes food

[12] See Food Standards Australia New Zealand initial assessment report (October 2004) http://www.foodstandards.gov.au/_srcfiles/A544_ISP_IAR.pdf and a response from the US FDA concerning the manufacturer's determination that the ISP preparation is Generally Regarded as Safe (April 2003) http://www.cfsan.fda.gov/~rdb/opa-g117.html

[13] "The status of food or feed produced by fermentation using genetically modified micro-organisms has to be clarified in the light of the recital no.16 of the Regulation. When the GM micro-organism is used as a processing aid, the food and the feed resulting from such production process are not to be considered as falling under the scope of the Regulation" [Extract of report from the Commission to the Council and the European Parliament on the implementation of Regulation (EC) no 1829/2003 of the European Parliament and of the Council on genetically modified food and feed (October 2006). See under item 10 at: http://eur-lex.europa.eu/LexUriServ/site/en/com/2006/com2006_0626en01.pdf]

[14] See under Item 7 at: http://ec.europa.eu/food/committees/regulatory/scfcah/toxic/summary23_en.pdf

[15] A summary of the information required of applications for the placing of food/feed products derived from GMMs on the market is provided in Section E Table 1 of the guidance document (pp52-58): http://www.efsa.europa.eu/etc/medialib/efsa/science/gmo/gmo_guidance/gmo_guidance_ej374.Par.0001.File.tmp/gmo_guidance_ej374_gmm.pdf

produced using GMMs irrespective of whether or not they fall under regulation 1829/2003. This guidance document describes three distinct groups of genetically modified microorganisms (GMMs). The ISP Type III HPLC 12 preparation would be classed as a group 2 GMM *"Complex products derived from GMMs but not containing viable GMMs nor unit length of any cloned (foreign) open reading frames (e.g. lysed cell extracts, some feed enzymes, wine, some beers, etc.)"* as, although it has been partially purified, the composition of the preparation has not been fully defined. A summary of the information required of applications for the placing of food/feed products derived from GMMs on the market is provided in Annex 1 below, with an indication of the corresponding sections of the application dossier.

I Specifications of the novel ingredient (NI)

Information on this aspect is provided on p. 10-12 of the application dossier

8. The novel food ingredient (NI) is a yeast-derived preparation containing a particular type of ISP known as ISP type III HPLC 12. Isoform HPLC 12 (ISP III-12) is the most functionally active form of type III ISP *in vitro* and is composed of 66 amino acids.

9. The NI is a light brown liquid and consists of ISP III-12 protein, glycosylated ISP III-12, and other components derived from the fermentation (proteins and peptides from yeast, sugars, acids and salt). The concentrate is stabilised with 10mM citric acid buffer.

10. The NI is produced according to Good Manufacturing Practice and the applicant has confirmed the following specification:

    - Assay – Not less than 5g/l active ISP type III HPLC 12
    - pH – 3.0 +/- 0.5
    - Ash – Not more than 2%
    - Heavy metals – Not more than 2mg/l

11. The applicant has provided compositional data on five commercial batches of the NI and data on one batch of concentrated NI in table 2 of the application dossier. Some key parameters from the commercial batches are summarised in the attached table A.

12. The applicant has stated that any variations observed between the batches are due to the concentration step employed during the production. The differences between the quantifiable and total solids are reflective of the cumulative variability inherent in the large number of analytical techniques used for characterisation. The

analysis demonstrated a minimum mass balance of 97.9% (w/w) and the applicant has concluded that all batches of the NI were found to be homogenous.

13. The applicant has stated that the NI is stable at -20°C for extended periods without preservatives. The final commercial material will be shipped in frozen sealed containers and the recommended storage time will be 6 months.

14. The applicant was asked to provide further information on the variability between batches of the ISP preparation, including the extent and pattern of glycosylation. The applicant indicated that, compared with other yeast strains, the GM yeast strain used to produce the NI has a limited ability to glycosylate proteins, resulting in 52 to 65% of ISP III-12 proteins in the NI being unglycosylated. The amino acid sequence of the ISP III-12 has 8 theoretical sites for O-glycolysation. The applicant provided liquid chromatographic-mass spectroscopic analytical results on commercial batches of the NI showing that the pattern of glycosylation is constant between batches and has been shown to be unaffected by either process or media changes. The applicant has also provided results from gel filtration chromatography on commercial batches of the NI indicating that 40% of the total ISP III-12 is glycosylated, of which 75% in glycoform I and 25% in glycoform II. The applicant highlighted that the glycosylated ISP III-12 is inactive and only the non-glycosylated ISP III-12 can bind to ice crystals. The applicant was of the view that the presence of glycosylated ISP III-12 in the NI will not affect its binding properties. In response to a request by the ACNFP, the applicant has also confirmed that the inactive glycosylated form of ISP protein has no function in the preparation. The application draws a parallel with the manufacture of food enzyme preparations, which are generally subjected to minimal processing in order to maintain high functional activity, resulting in varying degrees of purity. The applicant also points out that an extensive test regime has been carried out on the complete ISP preparation to ensure that it is safe for human consumption.

Discussion: *The Committee was satisfied with the applicant's explanation on the homogeneity of the NI (see paragraph 12 above). In response to the Committee's questions about the reason for glycosylated proteins being present in the NI, the applicant explained that these were inactive and that the partial purification process is designed to retain the maximum functional activity in the preparation. The Committee therefore accepted the applicant's proposed specification for the NI. The Committee also noted that the complete ISP preparation has been submitted to toxicological tests to verify that it is safe for human consumption (See section XIII).*

II. Effect of the production process applied to the novel food

Information on this aspect is provided on p. 13-14 of the application dossier

15. The production process involves fermentation with a genetically modified food grade yeast (*S. cerevisiae*) in sealed fermentation vessels (i.e. under contained use conditions). The applicant states that all steps in the production process are commonly used throughout the food industry. The 3 main steps are as follows:

- Fermentation – the volume is scaled up in stages to the final production volume and protein production is then induced. ISP is secreted into the medium during a controlled phase of slow growth;

- Cell removal – after fermentation the medium is filtered by microfiltration or filter press leaving a yeast cell free liquid. The yield and purity of the protein is increased by washing the remaining biomass with water;

- Concentration – cell removal is followed by an ultrafiltration step which retains all material above 1kDa, including ISP which is 6kDa, but removes small molecules. The product is then packaged and stored in frozen sealed containers.

Discussion: *The Committee was satisfied with the applicant's proposed production process for the NI.*

III. History of the organism used as a source of the novel food

Information on this aspect is provided on p. 16 and Appendix 7 of the application dossier

16. The parent organism *Saccharomyces cerevisiae* has been widely used in the food industry for fermentation purposes for a very long period. The specific yeast strain used for production of ISP, a derivative of strain CEN.PK, has been classified in the Netherlands, under Council Directive 90/219/EC[16], as belonging to Group 1 AB. The applicant also noted that commercial production of ISP for markets outside Europe commenced in the second quarter of 2003.

Discussion: *The Committee was content with the information provided on the history of the GM Saccharomyces cerevisiae strain used by the applicant as a source of the NI.*

[16] Council Directive 90/219/EC of 23 April 1990 on the contained use of genetically modified micro-organisms

IV. Effect of the genetic modification on the properties of the host organism

Information on this aspect is provided in Appendix 1 of the application dossier

17. The expression vector contains a synthetic gene coding for ISP type III HPLC 12 originating from ocean pout. This ISP has the same amino acid sequence as the ocean pout ice protein, but the nucleotide sequence has been engineered to reflect optimal codon usage in yeast, thus maximising expression in this host.

18. The vector used to introduce the ISP expression cassette was designed to integrate the expression cassette into the ribosomal DNA (rDNA) of the yeast genome. The resulting yeast strain, CENPK338, contains a multicopy expression cassette inserted at the rDNA locus with no antibiotic resistance markers and no bacterial or fish DNA.

19. The applicant was asked to provide additional data on the molecular characterisation of the insert in the GM yeast. The additional molecular data provided included a more detailed description of the vector, the insertion event and its characterisation. Unlike most eukaryotes, insertion of transformed DNA into the yeast genome occurs through homologous recombination. In addition, the efficiency of targeting is increased in direct proportion to number of copies of the target gene. The integration system used by the applicant exploits these two features of homologous recombination in yeast by targeting the vector to the multicopy ribosomal DNA locus. After targeted integration into the yeast genome the copy number of the expression cassette was increased by selection under growth conditions that favoured yeast cells with multiple copies of the DNA insert.

20. Southern blotting (using a LEU2 *BstE2-Eco*RV DNA fragment as a probe) revealed two bands of the expected size, with a high intensity band of 6.2Kb representing the multicopy expression cassette and a faint band of 2.2Kb representing the chromosomal LEU2 gene. The copy number of the 6.2Kb fragment was estimated at 30-50 copies. The absence of any other bands was interpreted as indicating that the expression cassette was integrated exclusively as tandem repeats. PCR of the flanking sequences using appropriate 5' and 3' primer pairs for the rDNA locus and the insert revealed bands of roughly the expected size for the 2 flanks; their size and identity was confirmed by cloning and sequencing. The absence of the ampicillin selectable marker was also confirmed by PCR.

21. Following the Committee's consideration of the above information, the applicant was asked to provide further data to demonstrate the absence of secondary integration sites in the genome of the host organism and on the sequence analysis of the flanking regions of the

insertion site(s) to check whether this revealed the creation of any potential open reading frames in these regions. The applicant has not found any secondary integration sites in the genome of the *S. cerevisiae* used for producing the ISP preparation. The applicant provided a figure showing restriction maps of the DNA structure generated on integration of the cassette and the fragments detected. Results obtained using five different restriction enzyme digests did not demonstrate the presence of a secondary integration site and the applicant was of the view that it is unlikely that this site would be masked, following this digestion. The applicant concluded that the rDNA locus was the sole location for integration of the expression cassette. Finally, the applicant also highlighted that the mechanism of integration regenerates the existing NTS1 sequence in rDNA, as confirmed by sequencing of boundary fragments. Integration therefore did not lead to generation of any additional open reading frames.

Discussion: *The Committee agreed that the tests carried out by the applicant had confirmed that the inserted DNA had been integrated at the expected site. The Committee was reassured by the further information provided by the applicant which showed that there was only one integration site and that no additional open reading frames were generated.*

V. Genetic stability of the GMO

Information on this aspect is provided in Appendix 1 of the application dossier

22. Strain stability was measured after more than 70 generations of growth under non-selective conditions. The following parameters were compared:

- Cell viability;
- Presence of the ISP gene (as detected by PCR);
- Structure of the integration site (as revealed by Southern blotting);
- Protein expression levels (under inductive growth conditions).

23. The applicant states that no differences were found for any of the parameters measured after the period of growth used for comparison.

Discussion: *The Committee was content with the information provided by the applicant on the genetic stability of the genetically modified yeast used for the production of the NI.*

VI. Specificity of expression of novel genetic material

Information on this aspect is provided in Appendix 1 of the application dossier

24. Expression of the ISP is under the control of an inducible pGAL7 promoter that only permits high levels of expression of the protein in the presence of galactose. Expression is repressed during growth in the presence of more than 0.5% glucose.

    Discussion: *The Committee noted the above information and did not raise any concerns.*

VII. Transfer of genetic material from GM microorganisms

Information on this aspect is provided in Appendix 1 of the application dossier

25. The applicant has tested the ISP preparation for contamination with DNA derived from the inserted ice structuring protein gene using an ISP gene specific PCR assay. No DNA contamination was detectable using this approach. The detection limit was estimated at 2×10^{-10}g ISP plasmid DNA/g of lyophilised ISP protein preparation.

    Discussion: *The Committee was satisfied that no DNA derived from the ISP gene inserted in the GM baker's yeast had been detected in the NI, at the limit of detection of the PCR method used.*

VIII. Ability of the GMM to survive in and colonise the human gut

Information on this aspect is provided in Appendix 1 of the application dossier

26. The production process is designed to remove all yeast cells from the ISP preparation and the final product should not contain any GM microorganism that could survive in or colonise the human gut.

    Discussion: *The Committee was content that there will be a filtration step within the production process to remove the GM yeast cells. The GMM will therefore not be present in the NI. The Committee noted that yeast proteins will however be present (see section XIII).*

IX. Anticipated intake/extent of use of the novel ingredient

Information on this aspect is provided on p. 16-19 of the application dossier

27. The applicant intends to use the NI in edible ice products to improve their nutrition profiles, organoleptic properties (taste and mouthfeel) and stability. The term "edible ices" encompasses ice cream, including dairy ice cream, milk ice, water ice, fruit ice, sorbets, frozen desserts and similar products such as iced smoothies. The level of ISP will not

exceed 0.01% by weight and will more commonly be less than 0.005% in the final product. As the ISP comprises 5-8% of the commercial product, the level of addition of the ISP preparation or the NI will be up to 0.2%.

28. The anticipated intake of ISP Type III HPLC 12 from its use in edible ices has been calculated using the latest UK NDNS data for children, young children and adults. Estimates are for consumers only, which means that only those who have consumed ice cream at some point during the survey period are included.

29. Results are given as daily edible intakes estimated as grams per day. Based on the information given the applicant estimates that boys aged 11-14 have the highest potential intake of edible ice per day with a high level (97.5th percentile) intake of 99 g/day. Using the maximum proposed level of inclusion of the NI and the average recorded body weight for this group of 47 kg, the estimated daily intake is 0.21mg of ISP type III HPLC 12/kg body weight. The applicant's estimates for each age group are presented in table B.

30. The NDNS surveys were carried out in 4 waves, covering January to March, April to June, July to September and October to December and the applicant has taken seasonal differences into consideration by providing estimates for each of the waves. This has found that, at the 97.5th percentile, for adults and children, there was only a small difference between the highest and the lowest consumption estimates, suggesting there is little change amongst those who consume edible ices in each season. However, there is a larger difference between the January to March wave and the June to September wave in the survey of young people (ages 4-16), where high level consumption (97.5th percentile) increases from 58 to 80 grams/day.

31. In order to complement the information provided in the original dossier, which gave seasonal data intake estimates for ISP from its use in edible ices only for the combined 4-18 age group, the UK Competent Authority asked the applicant to provide a breakdown of these estimates for the age bands 4-6 years, 7-10, 11-14 and 15-18, using the latest UK NDNS data (see below). The applicant provided the estimates of the daily consumption of edible ices by young people, broken down by both season and age (see Table C).

32. Although these estimates of high level consumption are less robust due to the relatively small number of consumers in each sub-group, the data show that the highest estimated intake, on a body weight basis, is in 4-6 year old children during the summer months (equivalent to 0.38. mg of ISP III-12 per kg bodyweight per day). Although this exceeds the highest estimates mentioned in the application dossier, the applicant points out that there is still a factor of 1500 between this and the NOEL of 5.8 g/kg bw/day observed in the animal feeding studies (expressed as ISP III-12).

33. The applicant has also estimated daily intakes of ice cream for the Netherlands using the 1997-98 Dutch National Food Consumption Survey and for France using CREDOC, Enquête individuelle et nationale sur les consommations alimentaires (INCA, 1999). In the Netherlands, the highest consumption of ice cream is found in adults, where high level consumption (95th centile) is 100g/day[17]. Ice cream consumption recorded in the French survey is lower, with an average value of less than 10 grams/day in all age groups.

    Discussion: *The Committee considered that the consumption of the NI at the proposed levels of incorporation on edible ices did not raise any specific concerns.*

X. Information from previous human exposure to the novel ingredient or its source

Information on this aspect is provided on p.16 of the application dossier

34. ISP occur naturally in the blood of fish living in areas where the sea freezes, such as cod and herring, and so are normally consumed in the diet. They are also found in edible plants such as oats, rye, barley, wheat, carrot, potato, taproot and leaves of Brussels sprouts. However, despite their similar functionality, ISP have a range of different structures and it is not possible to draw any meaningful comparisons with the NI.

35. Although ocean pout, the fish from which the ISP that this application refers to was originally isolated, has no history of consumption in the European Community, it is consumed in North Eastern USA. The applicant suggests that eating a 200g portion of ocean pout would result in an intake between 120 and 420 mg of ISP type III. This is higher than the estimated daily intake from edible ices (see above).

36. In addition to the ISP and its glycosylated counterpart, the NI contains other components derived from the fermentation. *Saccharomyces cerevisiae* has a very long history of use in food production and there is therefore a long history of consumption of the yeast itself and its fermentation products.

37. The applicant states that edible ices containing the NI have been on the market in the USA since the second quarter of 2003 with no reported consumer issues. Similar products have also been on sale in other countries such as the Philippines since 2004.

    Discussion: *The Committee was content with the information provided on previous human exposure to the NI and its yeast source.*

[17] Note: The Dutch values are averaged over only 2 days, compared with 7 days in the British surveys (or 4 days for pre-school children). On statistical grounds it is to be expected that the observed high level consumption of most foods will decrease as the survey period increases.

XI Nutritional information on the NF

Information on this aspect is provided on p.21 of the application dossier

38. As the NI will be used in edible ices at a level not exceeding 0.2% by weight (equivalent to 0.01% of the ISP component), the applicant has stated that no nutritional implications are expected. The NI's protein sequence is comprised of amino acids which are commonly found in the human diet and for this reason it would be digested as a protein according to normal metabolic processes and will not have any significant effect on total protein intake. The NI would not displace existing ingredients, although its use might facilitate the manufacture of ice cream products with a reduced fat content.

    Discussion: *The Committee was satisfied with the nutritional information provided for the NI.*

XII. Microbiological information on the novel food

Information on this aspect is provided on p.21-22 of the application dossier

39. The microbiological specification for the NI is as follows:

Total microbial count	<3000/g
Coliforms	<10/g
Listeria spp.	Absent in 25g
Salmonella spp.	Absent in 25g
Yeast and mould count	<100/g (GM yeast absent by test)
Staphylococcus aureus	<10/g
Bacillus cereus	<100/g

40. Table 7 in the dossier summarises the microbiological analysis of 10 commercial batches of the NI.

41. The microbiological safety of the edible ices containing the NI will be ensured by using the accepted principles of good manufacturing practice and conditions for processing and distribution currently applied to edible ices. The applicant considers that no additional controls will be necessary.

    Discussion: *The Committee was of the view that the microbiological safety of the NI had been demonstrated.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p.23-71 of the application dossier

42. The applicant has carried out an evaluation of the general toxicity and genotoxicity of the NI. The potential allergenicity of the NI was also assessed.

(a) Toxicological and genotoxicological assessments

Information on this aspect is provided on p.23-30, Appendices 6 and 10-15 of the application dossier

43. The applicant has provided details of a number of toxicological and genotoxicological studies carried out on the NI. The results of these studies are presented in the attached Table D. To increase their sensitivity these tests were conducted on a specially prepared batch of the NI, designated 201008, which was subjected to an additional concentration stage using ultrafiltration to remove excess water and low molecular weight components. The applicant was asked to provide additional information on batch 201008 of the NI regarding the way it was prepared and how its composition compares with the commercial product. The applicant explained that the final stage of the production process of the NI involves ultrafiltration with Synder spiral wound membrane modules (1 kDa). Batch 201008 is obtained by continuing the ultrafiltration for longer to obtain 30g/L of ISP III-12. Compositional comparison of batch 201008 with other batches of the NI is provided in table 2 of the dossier. The applicant has confirmed that the additional ultrafiltration does not modify the NI, as shown in study report AC000082 (Appendix 4 of the dossier).

44. The applicant concludes that the NI does not present any toxicological or genotoxicological potential.

(b) Allergenicity assessment

Information on this aspect is provided on p.30-66, Appendices 17-20 (study reports), Appendices 20 and 22 (publications)

45. A summary of the tests assessing the potential allergenicity of the NI is given in table 9 (Annex 1, p.31). The results of these tests are summarised in the attached Table E.

46. The applicant concludes that the NI is safe for both fish-allergic individuals and other consumers.

47. The applicant was asked to provide further details on the amino acid sequence analysis of ISP III-12. The applicant has therefore explained that the original amino acid sequence analysis of ISP III-12 against public protein databases was carried out in 2001/02. This analysis generated some false positives and was not repeated. In 2005, the amino acid sequence of ISP III-12 analysis was analysed again using a

customised allergen database (FARRP AllergenOnline database) and a general protein database (NCBI non-redundant database). This analysis did not reveal any significant sequence alignment with known allergenic proteins. The applicant concluded that ISP III-12 is unlikely to be a food allergen.

48. The applicant was also asked whether any information exists on the potential for the GM *Saccharomyces cerevisiae* proteins present in the preparation to induce allergic reactions in individuals sensitised to *Candida* 'yeast' or other fungi. The applicant indicated that sensitisation to yeast proteins most occurs via the respiratory tract and via the skin, and there is no evidence to indicate that it arises from the consumption of foods and drinks containing *S. cerevisiae*. This conclusion is supported by the fact that the three allergens in *S. cerevisiae* namely enolase, manganese super-oxide dismutase and cyclophin have only been associated with inhalant and/or skin allergies. It is recognised that people with atopic dermatitis which is associated with allergic reaction to yeasts such as *Candida albicans, Pytirisporum ovale* and *Malassezia furfur* are likely to cross-react to *S. cerevisiae* proteins when challenged in skin prick tests or RASTs. The applicant however refered to conclusions from Kortekangas-Savolainen et al (1994) that "the IGE-mediated allergy to baker's yeast should not lead to the denial of bakery, brewery and wine products".

(c) Potential yeast (Saccharomyces cerevisiae) allergenicity assessment
Information on this aspect is provided on p.48-51 and table 16 of the application dossier

49. The applicant notes that three proteins identified in *Saccharomyces cerevisiae* are associated with inhalant and/or skin allergies and adds that "all the fish allergic subjects who were skin prick test positive to yeast in the above studies are able to consume foods containing yeast without adverse reaction" (see table 16, p.51). The applicant is therefore of the opinion that the yeast component of the NI does not pose a clinically significant allergic risk.

Discussion: *The Committee was satisfied with the toxicological assessment carried out by the applicant on the NI which showed that it is safe for human consumption at the proposed level of use. The Committee particularly discussed the following points:*

- ***Inflammatory potential of the NI*** *– during our public consultation on this application, a member of the public suggested a need to conduct studies to test long-term inflammation in both young and older animals. The Committee asked for expert advice on this point from specialists in animal pathology and immunology of the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment. They were of the view that the applicant had carried out all the appropriate studies needed to assess potential immunogenicity. The 90-day study did not show*

any indication of any effects on the immune system, whether inhibitory or stimulatory, and there were no clinical signs of inflammatory responses that might justify further investigations in this area. The Committee therefore concluded that the NI did not have any inflammatory potential.

- ***Animal models of sensitisation*** *– The Committee was of the opinion that animal models of sensitisation had improved in recent years and that the quote in the dossier from the 2001 WHO Rome conference to the effect that, "such models were at too early a stage of development to generate data for risk assessment", was no longer valid. The Committee discussed the value of having a study of sensitisation using the ISP preparation on an appropriate animal model and concluded that, in this case, this additional information was not necessary.*

- ***Amino acid sequence homology of ISP Type III-12 with A.niger superoxide dismutase*** *– The Committee noted that reference in the application to Baderschneider et al's (2002) findings that a match over a very short part of the amino acid sequences between a superoxide dismutase (allergen Asp f6) from Aspergillus fumigatus and ISP Type III was not significant and the Committee asked for an external expert view on that point. The expert's view was that the similarity between ISP type III and AspF6 was very low and it is very unlikely that Aspergillus allergic individuals will react to ISP. The Committee therefore concluded that the NI will not induce a reaction in Aspergillus allergic individuals*

- ***Fish allergy*** *– The Committee queried whether the results from tests on cod-allergic people were sufficiently representative of fish allergy in general. The Food Standards Agency's allergy experts indicated that sera from cod allergic subjects are considered to be a relatively good candidate for assessment of whether the NI is likely to bind IgE of fish allergies. This is because of the high homology of parvalbumin (the major fish allergen) across fish species. Fish allergic individuals can be mono-sensitised to other non-parvalbumin allergens in fish, such as collagen, but this is relatively rare and it seems unlikely, although not impossible, that the non-parvalbumin allergens would cross-react with the ISP. Further, as cod allergic subjects, many of which also showed positive SPTs to ocean pout, eel pout and eel (indicating cross-reactivity among these species), did not react to the ISP preparation it seems unnecessary to extend the tests to subjects with other fish allergies besides cod. The Committee concluded that using the cod allergic individuals in Phase I of the assessment of the allergic potential of the ISP preparation is representative of the fish allergic population.*

- ***Yeast allergy*** *– The Committee did not agree with the applicant that the yeast proteins present in the ISP preparation did not present any potential allergenic risk and recommended that the labels of products containing the ISP preparation should indicate that it is derived from a yeast source.*

Labelling

Information on this aspect is provided on p.11 of the application dossier

50. The applicant proposes to describe the NI as "Ice Structuring Protein" in the list of ingredients of edible ices, consistent with other ISP-containing products on the market outside the EU.

Discussion: *The Committee considered whether the NI should be labelled as derived from a GM source. It was stated in a recent Commission report[18] that ingredients produced by fermentation using genetically modified micro-organisms not present in the final product do not fall under the scope of legislation on GM food and therefore do not need to be labelled as GM under this specific piece of legislation. This conclusion is shared by the Food Standards Agency and by the responsible authorities in other Member States and it can be applied to the NI, as the yeast cells are removed from the final product.*

The Committee was aware that other food ingredients derived from GM micro-organisms, such as enzymes used as processing aids and some highly-refined vitamins and amino acids, are not labelled to indicate their source. Nevertheless, the use of a synthetic gene sequence and the presence in the NI of a significant proportion of cellular by-products from the fermentation process such as yeast proteins (as noted in Section VIII above) made this a special case and the committee felt that the omission of this information through the absence of labelling could be potentially misleading to consumers.

The Committee therefore recommended that information should be provided to consumers indicating that the ingredient is manufactured using a GM yeast. This could be achieved either through information provided on food packaging or possibly via other easily-accessible routes, for example, via a reference to a website and the manufacturer's telephone careline.

The Committee noted that there was some misunderstanding among members of the public as to the source of the NI. Some think it to be a fish product that is therefore unsuitable for fish allergic individuals and vegetarians. The NI is not extracted from fish but from a non-

[18] Section 10 of the Report from the Commission to the Council and the European Parliament on the implementation of Regulation (EC) No 1829/2003 of the European Parliament and of the Council on genetically modified food and feed, COM(2006) 626, October 2006. http://eurlex.europa.eu/LexUriServ/site/en/com/2006/com2006_0626en01.pdf

animal source (yeast), which has been genetically modified by inserting a synthetic gene that provides a "blueprint" for a protein that has the same structure as one that is found in a type of fish. This confusion highlights the need for clear information about the NI to be made available to the public.

Overall Discussion

51. The information supplied by the applicant offers sufficient reassurance that the consumption of the NI in edible ices does not give rise to any toxicological or allergenic concerns, other than those associated with the presence of yeast proteins.

52. Regarding the labelling of the product, the applicant needs to comply with the Food Labelling Regulations 1996 (as amended). They should ensure that the labelling and presentation of the products adequately informs the consumer, particularly in relation to its consumption by yeast allergic individuals.

Conclusion

53. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by Unilever that the range of uses for its ice structuring protein preparation is acceptable, subject to the applicant's adherence to the proposed specification and the production parameters described above. The Committee recommends that products containing the ingredient should be labelled to indicate that it is derived from yeast. In order that consumers should be adequately informed and are not misled, the Committee also recommends that information should be provided to consumers in an easily-accessible format indicating that the ingredient is manufactured using a GM yeast.

July 2007

Annex 1

Comparison of requirements described in EFSA guidance on the risk assessment of genetically modified microorganisms (May 2006) against the data provided in the application dossier

A summary of the information required of applications for the placing of food/feed products derived from GMMs on the market is provided in Table 1 of the guidance document (pp52-58). The main categories are:

Category described in the EFSA guidance document	Corresponding section of the application dossier (see ACNFP/78/2)
Characteristics of the recipient or parental microorganism	Section III: History of the organism used as the source of the NF
Characteristics of the donor organism	Section X: Information from previous human exposure to the NF or its source *(Note: the ISP gene introduced into the production organism is synthetic, designed to code for the same protein that is found in fish)*
Description of the genetic modification process	Section IV: Effect of the genetic modification on the properties of the host organism
Information relating to the GMM and comparison of the GMM with its conventional counterpart	Section IV: Effect of the genetic modification on the properties of the host organism Section V: Genetic stability of the GMO Section VI: Specificity of expression of novel genetic material *(comparison between the GMM and its conventional counterpart is not applicable as there is no equivalent product from non-GM yeast)*
Information relating to the production process	Section II: Effect of the production process applied to the NF
Information relating to the production purification process	Section II: Effect of the production process applied to the NF
Description of the product	Section I: Specification of the NF Section XI: Microbiological information on the NF
Assessment of the presence of recombinant DNA and of the potential risk of gene transfer	Section VII: Transfer of genetic material from GM microorganisms Section VIII: Ability to survive in and colonise the human gut

Category described in the EFSA guidance document	Corresponding section of the application dossier (see ACNFP/78/2)
Comparison of the GM product with its conventional counterpart	(not applicable as there is no conventional counterpart)
Considerations for human health and animal health of the GM product (including toxicity and allergenicity)	Section IX: Anticipated intake/extent of use of the NF Section XI: Nutritional information on the NF Section XIII: Toxicological information on the NF

Tables

Table A: Composition of batches of the commercial the ISP preparation

Batch	200030	200034	200046	201024	201083
Total protein (g/litre)	15.0	14.3	16.4	23.7	31.5
ISP III-12 (g/litre)	5.5	4.8	5.0	6.2	8.4
Protein breakdown (% of total)					
ISP III-12	*36%*	*34%*	*31%*	*27%*	*27%*
glycosylated ISP III-12	*22%*	*18%*	*20%*	*23%*	*25%*
yeast protein	*23%*	*24%*	*22%*	*29%*	*32%*
peptides	*20%*	*24%*	*28%*	*22%*	*17%*
Total solids (g/litre)	34.5	41.0	39.7	73.0	77.7
Unquantified solids* (g/litre)	3.0	10.0	6.4	20.6	8.4
Unquantified solids (% of total)	9%	24%	16%	28%	11%

* Quantified solids = Total Kjeldahl protein + mannose + citric acid + minerals (Na, K, Mg, Ca, PO_4)

Table B: Consumption of edible ices by British consumers

	Consumption of edible ices recorded in NDNS surveys (grams/day)					
Age	1.5-4.5	4-6	7-10	11-14	15-18	19-64
Proportion of consumers	42.9%	61.1%	59.3%	49.6%	35.7%	27.3%
Median (M/F)	16/15	17/14	18/17	22/18	16/13	17/17
High level (97.5th centile) M/F	62/64	59/73	63/64	99/76	83/71	78/73

Table C: Consumption of edible ices by British children, by season

			Centiles of consumption of edible ices recorded in 1997 NDNS survey (grams/day)					
Age groups	Wave	N	5th	10th	50th	90th	95th	97.5th
4–6 yrs	1	42	2.14	6.43	14.86	31.14	32.29	39.71
	2	57	4.29	5.00	15.00	40.43	57.00	57.14
	3	61	5.43	7.57	16.57	38.43	59.43	76.29
	4	57	5.16	7.14	16.86	36.43	45.43	45.57
7–10 yrs	1	45	5.00	5.43	17.14	43.00	50.43	51.71
	2	72	6.86	8.57	20.50	42.00	60.00	63.00
	3	102	7.57	8.57	21.07	51.86	63.00	77.71
	4	68	7.00	8.00	15.86	33.90	45.43	58.43
11–14 yrs	1	44	4.29	4.71	17.93	50.71	58.29	62.29
	2	70	4.86	6.93	17.71	51.71	61.71	84.57
	3	73	7.29	9.14	21.57	58.57	80.86	83.14
	4	45	4.86	5.43	16.71	43.14	49.29	60.00
15–18 yrs	1	26	5.00	6.86	12.43	33.00	35.14	60.57
	2	27	5.66	5.71	17.00	54.86	62.43	80.86
	3	55	5.71	7.14	15.43	45.86	70.86	83.00
	4	31	6.00	7.00	15.71	39.29	77.86	85.57

Wave 1: Jan – Mar, Wave 2: Apr – Jun , Wave 3: July – Sep and Wave 4: Oct – Dec

Table D: Toxicological and genotoxicological studies on the novel ingredient

Appendix to application dossier	Test material	Tests	Result
Appendix 9	ISP Type III HPLC 12 preparation Batch 201008[1]	90-day sub-chronic oral toxicity test in rats, at doses equivalent to 58, 290 and 580 mg ISP per kg bodyweight per day	NOAEL is 580mg ISP Type III HPLC 12/kg bw/day, equivalent to 6.9 – 12.1g of the NI/kg bw/day[2]
Appendix 11	ISP Type III HPLC 12 preparation Batch 201008 FD[3]	Bacterial reverse mutation assay using 4 strains of *Salmonella typhimurium*	Negative on 3 strains False-positive on 1 strain due to contamination with other microorgnisms
Appendix 12	ISP Type III HPLC 12 preparation Batch 2010034	Bacterial reverse mutation assay using 4 strains of *Salmonella typhimurium*	Negative on all strains
Appendix 13	ISP Type III HPLC 12 preparation Batch 201008 FD[3]	*In vitro* chromosome aberration assay in human peripheral blood lymphocytes	Negative
Appendix 14	ISP Type III HPLC 12 preparation Batch 201008 FD[3]	Gene mutation assay at the thymidine kinase locus of mouse lymphoma L5178Y cells	Negative
Appendix 15	ISP Type III HPLC 12 preparation Batch 201008 FD[3]	*In vivo* rat bone marrow micronucleus assay	Negative
Appendix 16	AFP III HPLC 12 preparation[4]	Randomised placebo controlled human trial to evaluate single ingestion	No toxicity detected

(1) Batch 201008 is a concentrated form (-5-fold) of the commercial preparation. Compositional data for batch 201008 and for 5 standard commercial batches of the NI can be found in the application dossier, Table 2, p.12.
(2) Calculation of the NOAEL expressed as NI containing between 4.8% and 8.4% of ISP Type III HPLC 12 (application dossier, Table 2, p12).
(3) Batch 201008 was too dilute for use in genotoxicity and was therefore freeze-dried to obtain ISP Type III HPLC 12 preparation Batch 201008 FD. No difference in composition, except for the water content, was observed between these two batches (application dossier, Appendix 5)
(4) The applicant has explained that "Anti- Freeze Protein (AFP) III HPLC 12" is used in this study report as an alternative name for ISP Type III HPLC 12 (application dossier, p.6)

Table E: Tests on the potential allergenicity of the novel ingredient

Dossier reference	Test material	Tests	Result
Appendix 21	–	Amino acid sequence analysis using BLAST and FASTA computer programmes	No primary sequence similarity with any known allergens, including fish allergens
Appendix 18 Figures 7-9 Table 22	ISP Type III HPLC 12 preparation	Pepsin hydrolysis resistance	Most of the peptides <2.3kD Low probability that ISP Type III HPLC 12 could elicit reaction

(a) Phase I Studies in 20 fish allergic individuals (cod)

–	Eel, eel pout, ocean pout	Skin prick testing	Positive
Table 13 Figure 4	Ocean pout extract (2 mg protein/mL) Freeze-dried ISP III HPLC 12 preparation (20 ng/mL to 200µg/mL)	IgE binding *in vitro* – RAST inhibition	18/20 subjects had IgE against ocean pout No binding of IgE to freeze-dried ISP preparation
Table 13	Nine different concentrations (3.5-fold dilutions) of ocean pout extract (max = 0.2mg/mL) and freeze-dried ISP III HPLC 12 preparation (max = 10 mg/mL)	IgE binding *in vitro* – Basophil histamine release	Positive for ocean pout extract Negative for freeze-dried ISP III HPLC 12 preparation

(b) Phase II Studies in 22 fish allergic individuals

Table 14	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III Pure ISP Type III HPLC 12 preparation (no yeast proteins)	Skin prick testing	4 subjects reacted to both test materials These 4 subjects did not react to pure ISP Type III HPLC 12 preparation (no yeast proteins)
Tables 15 and 16 Figure 5	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III Pure ISP Type III HPLC 12 preparation (no yeast proteins)	IgE binding *in vitro* – RAST inhibition	8 subjects were positive to ISP Type III HPLC 12 preparation including yeast protein. These 8 subjects included 3 of the 4 subjects who reacted positive to the skin prick testing. All 8 subjects did not react to pure ISP Type III HPLC 12 preparation (no yeast proteins) No binding of IgE to freeze-dried ISP preparation
–	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III Pure ISP Type III HPLC 12 preparation (no yeast proteins)	IgE binding *in vitro* – *Basophil histamine* release to investigate positive skin prick test results	Positive for both materials Negative on pure ISP Type III HPLC 12 preparation (no yeast proteins)

(c) General allergy testing on 28 healthy adults

Table 17	ISP Type III HPLC 12 preparation	Antibody response to ingestion on 28 healthy adults without a history of previous consumption of ISP Type III with 8 controls	No observed clinical symptoms or biochemical changes associated with food allergy
Table 18	ISP Type III HPLC 12 preparation	Enzyme-linked immunosorbent assay (ELISA)	Negative
–	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III Pure ISP Type III HPLC 12 preparation (no yeast proteins)	Skin prick testing	1 subject positive to both materials but negative on pure ISP Type III HPLC 12 preparation (no yeast proteins)
Table 19	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III	IgE binding *in vitro* – RAST inhibition	Weak specific IgE response (peaking at week 4)
Table 20	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III	IgE binding *in vitro* – Basophil histamine release	Negative
Figure 6	ISP Type III HPLC 12 preparation including yeast protein Yeast fermentation supernatant excluding ISP Type III	IgE binding *in vitro* – immunoblotting	Negative

APPENDIX IV

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on an application under the novel food Regulation for glucosamine hydrochloride from *Aspergillus niger* as a novel food ingredient

Applicant: Cargill Incorporated

Responsible Person: Brent Rogers

EC Classification: 2.1

Introduction

1. An application was submitted by Cargill Incorporated on 14 August 2006 for the authorisation of glucosamine hydrochloride (HCl) from *Aspergillus niger* as a novel food ingredient. A copy of the application dossier was placed on the FSA website for public consultation.

2. Glucosamine is a naturally occurring amino-sugar that is a major component of complex proteins called glycosaminoglycans, which form a component of cartilage.

3. In August 2004, the Committee issued an opinion that Cargill's glucosamine HCl derived from A. *niger* was substantially equivalent to the shellfish derived glucosamine that was already on the market in food supplements and foods with particular nutritional uses (PARNUTs). The Commission was notified, and supplements and PARNUTs foods containing glucosamine from this source may now be legally placed on the EU market.

4. Cargill now seeks approval to market its fungal glucosamine HCl in a range of products, mainly beverages and fermented milk-based products at levels that would provide 750mg per daily serving.

5. The application for authorisation of this fungal glucosamine HCl was prepared pursuant to Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients. The novel ingredient (NI) has been classified as a complex novel food from a non-GM source with a history of food use of the source in the community (class 2.1). The information presented in the dossier is structured accordingly and is considered below.

I. Specification of the Novel Ingredient (NI)

Information on this aspect is provided on p.9-14, and Appendix 1 and 1A of the application dossier

6. The NI contains a minimum of 98% glucosamine hydrochloride and complies with the monograph for glucosamine hydrochloride in the US Pharmacopoeia-National Formulary (USP-NF). (This information was omitted from the original dossier, but was later added at Appendix 1A). There are 12 tests outlined in this monograph which are listed in Table I-1. Analytical results for 5 non-consecutive batches of the NI are summarised in Table I-2 and indicate that the NI meets the required specification.

7. An additional analysis has been carried out for pesticide residues and aflatoxins. All levels are within prescribed limits.

   Discussion: *Members accepted that the product met with the USP-NF specification.*

II. Effect of the production process applied to the NI

Information on this aspect is provided on p.15-20 of the application dossier

8. The production process is comparable to the one used to isolate shellfish derived glucosamine HCl and is similar except for the source of the raw material. Briefly, the chitin containing biomass from *A. niger* is hydrolysed by heating in the presence of hydrochloric acid then filtered to remove solid impurities. The remaining glucosamine is then crystallised, centrifuged and dried before packaging.

9. During the public consultation a question was raised regarding the likelihood of the production process employed giving rise to the formation of process contaminants such as acrylamide and chloropropanols. Acrylamide was ruled out because the conditions employed were not conducive to its formation, but Members were asked to consider the likelihood of chloropropanols such as 3-monochloropropane-1,2,-diol (3-MCPD), being generated during the acid hydrolysis stage of the process.

   Discussion: *Members accepted that the production process was the same as the one that was currently being used for the novel ingredient which is sold in dietary supplement form, and was very similar to the process used for to obtain glucosamine from shellfish. The Committee considered the possibility of 3-MCPD, being present. 3-MCPD is known to be formed through the action of concentrated hydrochloric acid on lipids and it has previously been found in foods such as acid-hydrolysed vegetable protein. The applicant explained the fungal biomass has relatively low lipid content (0.5% dry wt) and that the subsequent steps in the purification process would be expected to*

remove any impurities. As 3-MCPD is water-soluble, any residues would be removed with the mother liquor during the crystallisation and the final stage, in which the crystals are washed with water, would also remove any additional impurities. The Committee concluded that the production process did not give any cause for concern.

III. History of the organism used as the source of the NI

Information on this aspect is provided on p.20-21 of the application dossier

10. The source organism is a strain of the fungus *Aspergillus niger* that is referred to as non-toxic and non-pathogenic for humans and other animals. The dossier refers to *A. niger* as having a history of safe use generally in food production since the 1920's. The strain used to produce the NI has been used in the US and other countries for citric acid production since 1993.

    Discussion: *Members accepted that A. niger was widely used in the food industry, and that there were no concerns regarding the general safety of the fungus. However, the Committee expressed concern that there was a low level risk of allergenicity if proteins were present in the final product. (see Paragraph 40 below).*

IX. Anticipated intake/extent of use of the NI

Information on this aspect is provided on p.22-31 of the application dossier

11. The applicant intends to use the NI in fruit juice and fruit juice products, dehydrated instant drink mixes, fermented milk based products such as yoghurts and fromage frais, sports drinks and iced tea drinks, at levels that would provide 750mg per daily serving. These categories of foods which will be fortified with the NI are intended for population groups that seek nutritional support to maintain healthy joints. These groups include older people and sportsmen or women. The applicant is of the view that these food categories are intended to be consumed as an alternative to, rather than as well as, food supplements or PARNUTs foods. The proposed uses are summarised in Table IX.2-1 of the application dossier.

12. Although these would not form part of the target population, the applicant also provided intake estimates calculated using the UK NDNS data for young children (1997), schoolchildren (1992-1993) and adults (1986–1987). Intakes have been calculated for 'all persons' (i.e. all people in the surveyed population) and 'all users' (i.e. all people in the surveyed population who have consumed the foods that might contain the NI).

13. Figures in Table IX.3-1 for 'all users' show that on a mg per person per day basis the theoretical highest mean and 95th percentile intakes of approximately 543 mg per day and 1542mg per day of the NI may occur in young people/children between the ages of 4 and 10. This "worst case" estimate is based on such children being regular consumers of all of these products, which the applicant states would not be the case. In the other population groups intakes are similar with mean daily intakes consumption ranging from 473 to 534 mg/day and 95th percentile intakes ranging from 1270 to 1542 mg/day.

14. Calculations on a body weight basis also show that children/young people have the highest potential level of consumption at 19.05 mg/kg per day for all person consumption and 21.72 mg/kg per day for all user consumption. As above, intakes are similar for different age groups with the greatest potential consumption being in male teenagers. Among the proposed beverage uses, fruit juices and yoghurt are the major contributors to intake of the NI in all groups.

15. Based on these intake estimates, the applicant has concluded that the safe endpoints indicated from all safety studies (see Section XIII below) would not be exceeded by consumption of the NI at the recommended maximum levels.

16. The Food Standards Agency notes that the market for the foods in the categories listed in Table IX.2-1 has changed markedly since the 1986–1987 NDNS data was collected. An Agency review using data from the more recent NDNS survey of British adults (2000) gave significantly higher estimates for mean and 95th percentile intakes of 1056 and 2792 mg per day respectively. The Committee noted these values and expressed concern that the estimates may be conservative since it was assumed that consumers would not also consume dietary supplements containing glucosamine. Members also expressed concern that appetising foods with added glucosamine may be consumed by children and that the applicant did not provide an adequate explanation of what they considered to be a safe upper level of consumption.

17. In response the Applicant provided a simplified list of food applications and use levels, as shown in the following table:

Product	Maximum levels of incorporation
Fruit juice and fruit smoothie type products	375 mg per 100 g
Soft drinks (including ready to drink iced teas)	300 mg per 100 g
Fermented milk-based products	750 mg per 100 g
Dried beverage mixtures	300 mg per 100 g
Sport Drinks	300 mg per 100 g

18. The applicant also emphasised that products containing the NI would be marketed as a support to joint health in adults and not marketed at children. The applicant noted that if the products were to be marketed at children then this would require the submission of a dossier under EU Health & Nutrition Claims legislation. The applicant was also of the view that even if there was occasional consumption by children (such as a child consuming a product intended for an adult in the home) then there was no reason to presuppose that this would be a risk to health. The applicant highlighted that the dietary supplements containing up to 1500mg glucosamine were widely available on the UK market, and that in addition to the metabolism of glucosamine being both well understood and tightly regulated in the body, there were also numerous scientific studies carried out demonstrating safe consumption at these levels and at levels of up to 3200mg/day. The applicant also noted that whilst the dietary survey data may indicate higher levels of intake, these were a 'worst case scenario' and realistically high levels would not exceed 500mg/day.

Discussion: *Members accepted the additional information as providing the necessary reassurance that high level consumption (in excess of 1500mg/day) was unlikely to occur on a regular basis, but remained concerned that high level consumption could have implications for adults with type 2 diabetes (both diagnosed and undiagnosed). (This issue is discussed in detail at Section XIII.)*

X. Information from previous human exposure to the NI

Information on this aspect is provided on p.32-34 of the application dossier.

19. The applicant is of the view that there is widespread consumption of the NI in the form of supplements throughout the world, including within the EU; however, there is no formally established maximum recommended daily intake for glucosamine. Examples of products currently on the market and the recommended daily intakes are given in Table X.1-1. The proposed foods containing the NI are intended to provide an alternative, and not an additional, source of glucosamine to supplements and PARNUTs foods.

    Discussion: *Members accepted that the NI, and its counterpart which is obtained from shellfish is widely available throughout the world. Members accepted that the purpose of the NI was to provide an alternative and not an additional source of glucosamine.*

XI Nutritional information on the NI

Information on this aspect is provided on p.35-37 of the application dossier.

20. The nutritional value of the NI is given in Table XI-1 of the application dossier. The NI has little nutritional value other than a source of carbohydrate and its inclusion in various food categories is intended to provide an alternative source of glucosamine

    Discussion: *Members accepted that the nutritional properties of the NI did not give cause for concern.*

XII. Microbiological information on the NI

Information on this aspect is provided on p.38-39 of the application dossier.

21. The NI meets the USP-NF microbiological specification, and microbiolgical food standards. The applicant demonstrates this by tabulating counts of yeast and moulds, total coliforms, *Escherichia coli, Staphylococcus aureus* and *Salmonella* in 5 separate batches of the product (Table XII.1-1). The results demonstrate that the necessary specifications have been met.

    Discussion: *Members accepted that the NI met the requisite microbiological specification.*

XIII. Toxicological information on the NI

Information on this aspect is provided on p.40-66 of the application dossier

(a) Toxicological evaluation of A.niger
Application Dossier p.41

22. The strain of *A. niger* used to produce the NI was selected based on its safety. The strain does not produce ochratoxin A and the absence of this mycotoxin from the final product is confirmed by the results of tests carried out and presented in Appendix 2 of the application dossier (Incorrect reference to Appendix 3 in the dossier).

(b) Toxicological evaluation for glucosamine

23. Much of the data by the applicant regarding the toxicology of glucosamine and its safety in humans is taken from a recent review of the literature and from a recent human study, the Glucosamine/ chondroitin Arthritis Intervention Trial (GAIT) study.

Glucosamine metabolism
Application Dossier p.42-43

24. Exogenous glucosamine is actively transported into cells by glucose transporters, a process that is facilitated by insulin. Glucosamine is a component of the hexosamine pathway, an important branch of glycolysis. Glucosamine metabolism is highly regulated by differing rates of transport into different tissues according to glucose transporter affinity.

25. Some animal studies suggest that glucosamine administration may produce insulin resistance and hyperglycaemia. However, most *in vitro* and animal studies have achieved blood and tissue levels 100 to 2000 times higher than would be expected with the glucosamine doses used in humans.

Absorption, Distribution, Metabolism and Excretion (ADME) studies
Application Dossier p.43-46

26. A number of ADME studies have been carried out in animal models and human volunteers and the results of these studies are comparable. Collectively, the studies indicate that a large proportion of orally administered glucosamine is absorbed but has a limited bioavailability as a significant proportion undergoes first pass metabolism in the liver. Consequently, tests in rats have shown that the blood levels of glucosamine after oral administration are only about 20% of those achieved by the intravenous route. Glucosamine is detectable in most tissues examined after oral administration to rats including the liver, kidney and joint cartilage.

Animal toxicity studies: acute (oral)
Application Dossier p.46-47

27. The LD_{50} of glucosamine for rats and mice exceeds 5000mg/kg and for rabbits exceeds 6000mg/kg. The NOAEL for the NI was determined by one rat study to be 5000mg/kg. Table XIII.2.2.1-1 summarises the single dose acute oral toxicity studies carried out on glucosamine.

Animal toxicity studies: subchronic and chronic (oral)
Application Dossier p.47-50

28. A number of studies in various animal species have looked at the effects of glucosamine over an extended time period (12 – 365 days). These studies are summarised in Table XIII.2.2.2-1. Based on these studies the NOAEL for rats and dogs (for free base glucosamine) has been established as at least 2130mg/kg and 1696mg/kg body weight/day respectively.

Animal toxicity studies: parenteral administration
Application Dossier p.51

29. The effects of intravenous (IV) or intraperitoneal (IP) administration of glucosamine has been examined in rats and mice. The LD_{50} data are summarised in the Table below.

Species	Rat		Mouse	
Route administered	IV	IP	IV	IP
LD_{50} (mg/kg bodyweight)	~1700	>5200	~1600	>6600

30. The rat model has often been selected for study as it is particularly sensitive to the effects of parenteral glucosamine administration on glucose metabolism. Of 14 reports reviewed, glucose metabolism was altered in 12, resulting in higher blood glucose levels, reduced uptake of glucose and decreased disposal of glucose. The dosage of glucosamine reported in these studies ranged from 240 to 9937 mg/kg. However, the reduced bioavailability of orally administered glucosamine means that the levels reached in the blood are typically only 20% of those reached through parenteral routes. Blood glucose levels were not significantly altered in studies where high doses of glucosamine (1000 to 2149 mg/kg bodyweight) were administered orally to rats, rabbits or dogs.

Animal toxicity studies: mutagenicity and genotoxicity
Application Dossier p.51-53

31. The applicant has carried out an *in vitro* study of the mutagenic activity of the NI using the *Salmonella- E. coli/*mammalian-microsome reverse mutation assay. In tests on 5 batches of the NI there was no increase in the mean number of revertants; this is in agreement with a previously published study, although there is also some evidence that glucosamine may have clastogenic[19] effects *in vitro*.

32. The applicant has also carried out an *in vivo* micronucleus assay in mice using the NI at doses up to 2000mg/kg. No clinical signs of cytotoxicity were found at the doses used. Based on these negative findings of genotoxicity *in vitro* and *in vivo* the applicant concludes that the NI is non-genotoxic. The applicant points out that a positive result was obtained in a mouse chromosomal aberration study using only a single dose. Weighed against the body of available evidence the applicant does not consider this result to be significant.

Human studies: clinical
Application Dossier p.53-57

33. The applicant has summarised the extensive literature on human clinical studies in Table XIII.2.3.1-1. In summary the applicant considers glucosamine to be well tolerated with no serious effects reported.

Human studies: adverse events
Application Dossier p.57-60

34. A number of non-specific symptoms are commonly reported in glucosamine supplementation trials. These include constipation, diarrhoea, nausea, dyspepsia, excessive gas, abdominal distension, abdominal cramps, headache and skin rash or pruritis. The studies in the literature reporting side effect data comparing glucosamine to placebo are summarised in Table XIII.2.3.2-1. In 12 of the 19 studies symptoms were less common in glucosamine treated subjects than those given placebo. Only two studies reported the reverse.

35. Further reviews of the side effects, effectiveness and toxicity of glucosamine are cited and data summarising these studies are shown in Tables XIII.2.3.2-1 and –2. A recently completed clinical trial, the largest to date, examining both efficacy and safety is cited as supporting the safety of chronic glucosamine supplementation. The Committee queried why the applicant had dismissed the findings of an *in vivo* study by Nguyen *et al.*, (2001) which indicated a higher proportion of subjects with adverse reactions than in other studies. In response, the applicant suggested that this could be attributed to the relatively high dropout rate and highlighted a comment by the

[19] Clastogenic = causing changes to chromosomes (e.g. breaks in chromosomes, change in chromosome number)

authors that of the nine individuals who dropped out of the study, only three of them dropped out for reasons that could be attributed to the study. The applicant also speculated that additional use of chondroitin sulphate in this study could have been a contributing factor. The applicant also noted that the adverse reactions reported were mild and were consistent with reactions to shellfish (the source of the glucosamine used in this study).

Human studies: objective endpoints
Application Dossier p.60-61

36. The results of 16 studies reporting various specific safety endpoints, including toxicological assessments, haematological and cardiovascular parameters are summarised in Table XIII.2.3.3.1. No adverse effects were reported for any of the parameters measured in any of these studies.

Human studies: glucosamine hydrochloride versus sulphate
Application Dossier p.64

37. There appears to be no evidence that there is any difference in the efficacy or safety of either form of glucosamine. The only difference that needs to be considered is the quantity of free base in each preparation.

Human studies: effects of glucosamine on glucose metabolism
Application Dossier p.62-63

38. Clinical trials reporting fasting blood glucose levels in subjects receiving glucosamine supplementation are shown in Table XIII.2.3.3-1. In total 18 studies, either directly or indirectly, have reported that glucosamine supplementation has no effect on fasting blood glucose levels in humans (see para 29 above). A review published in 2006[20] concluded that the data from these studies are limited and it remains to be determined whether long-term glucosamine intake has detrimental effects in patients with more severe diabetes. These authors recommended that patients initiating glucosamine supplementation should monitor their glucose levels closely. Further studies have appeared in the scientific literature after the dossier was drawn up, including one suggesting that a single oral dose of 1500 mg of glucosamine sulphate (equivalent to 970 mg of glucosamine base) may interfere with glucose metabolism in susceptible individuals[21], such as those with type 2 diabetes. In response to concerns raised by the Committee, the applicant provided a supplementary report which provided a critical review of the available literature on this issue.

[20] Stumpf JL, Lin SW (2006) Ann. Pharmacother. 40(4) 694-698,
[21] Biggee BA, Binn CM, Nuite M, SILbert JE, McAlindon TE (2007) Ann. Rheum. Dis. 66(2) 260-262.

Human studies: high intakes and long term use
Application Dossier p.63-64

39. The results of studies involving high intake or long term use of glucosamine are summarised. High intakes appear to be well tolerated and there was no difference in the frequency of adverse events in glucosamine-supplemented groups and placebo controls in long term studies.

Discussion: *Members accepted the toxicological studies provided by the applicant as being sufficient to demonstrate the general safety of the NI. Members also accepted the additional clarification regarding the adverse results noted in the study by Nguyen et al (2001).*

The Committee noted that the target population for products containing glucosamine would include middle-aged or elderly people, including a significant proportion of diabetics, including a number whose condition has not been diagnosed. The Committee was therefore concerned by the reports that glucosamine might affect glucose metabolism in diabetics. Members took note of the additional review provided by the applicant but were of the view that the available scientific studies were inadequate to determine the likelihood of a significant effect of glucosamine on glucose metabolism amongst individuals with Type 2 diabetes. Furthermore, a December 2006 opinion from the European Medicines Evaluation Authority[22] advised that this potential interaction should be highlighted to patients who are taking medicinal products containing glucosamine.

Members noted that glucosamine is currently on the market in the form of dietary supplements, but any concern over a possible effect in diabetics would be greater if it was added as an ingredient to a range of foods since adverse reactions were less likely to be picked up by clinicians than if the glucosamine was being consumed as a food supplement.

Allergenicity

Application Dossier p.65

40. An expert opinion on the potential allergenicity of the NI has been provided by an allergy specialist[23], who concludes that: there is no reason to be concerned about the possible allergenicity of the NI.

[22] [EMEA reference to be added]
[23] Professor S.L. Taylor of the University of Nebraska

41. Conventional methods for protein analysis cannot be used for the NI due to interference by the glucosamine. In order to demonstrate the absence of protein in the NI, the applicant therefore carried out SDS-PAGE analysis of a single batch followed by sequential staining of the gel with Sypro Ruby and Coomassie blue (Application dossier, Appendix 3).

42. Members were of the view that the use of SDS-PAGE gels was not the most sensitive way to measure protein levels in the novel ingredient. The Committee accepted that nitrogen-based methods could not be used but suggested the use of an alternative method such as Mass Spectrometry. The applicant highlighted that the production process employed used high temperature and acidity which was likely to denature any potential allergenic protein and noted that there had been no reports of allergenicity from sales of the NI as a supplement. The applicant subsequently provided LC-MS data demonstrating that the NI did not contain any protein.

    Discussion: *Members accepted that the LC-MS data provided adequate reassurance that the NI does not contain detectable amounts of protein.*

Proposed labelling

Information on this aspect is provided on p.10 & 33 of the application dossier

43. In the earlier application for substantial equivalence (see paragraph 3 above) the applicant agreed to label the product as "Non-Shellfish Glucosamine Hydrochloride" with a footnote referring to its source "from the fungus *Aspergillus niger*".

44. In this application the applicant requested reference to fungus be removed and proposed to simplify the labelling to, "Non-Shellfish Glucosamine Hydrochloride" with a footnote referring to its source "from *Aspergillus niger*". This was justified on the grounds that there is no trace of the organism in the final product and there is therefore no need to label on the grounds of allergenicity. Furthermore, the applicant pointed out that products such as citric acid and soya sauce, which are also manufactured by fermentation of *Aspergillus*, have a long and safe history of use and are not labelled to indicate their fungal source.

    Discussion: *The Committee noted the applicant's argument but remained of the view that the applicant should be encouraged to mention the fungal source of glucosamine when labelling the product*

Overall Discussion

45. The Committee noted that this NI had previously been considered by the Committee when the applicant had requested an opinion on the equivalence of the NI compared with the existing counterpart which is obtained from shellfish. Although the applicant had previously obtained a positive opinion on equivalence, this application was for a number of new food categories and as a full novel food application (Article 1 of (EC)258/97) and required greater scrutiny in order to determine whether the criteria for authorisation of a novel ingredient were met, namely that the ingredient must not:

    - Present a risk to the consumer
    - Mislead the consumer
    - Be nutritionally disadvantageous (compared with existing ingredients that it might replace).

46. The Committee considered that the available information is insufficient to reach a firm conclusion regarding the possible effect of the novel ingredient on glucose metabolism, which would be of particular concern for diabetic individuals. The Committee was satisfied with the safety of the novel ingredient in other respects, and saw no reason to change the previously agreed wording for labelling of this ingredient.

Conclusion

47. The Advisory Committee on Novel Foods and Processes is of the view that additional assessment is required in order to judge whether glucosamine hydrochloride, for use as an ingredient in a range of foods and beverages, meets the criteria for acceptance of novel foods and food ingredients.

June 2007

APPENDIX V

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Initial opinion on an application under the novel foods Regulation for baobab dried fruit pulp as a food ingredient

Applicant	Phyto Trade Africa
Responsible Person	Cyril Lombard
EC Classification	2.2

Introduction

1. An application was submitted by PhytoTrade Africa for the authorisation of baobab dried fruit pulp as a novel food ingredient. The UK Competent Authority accepted the application on 9 August 2006.

2. Baobab dried fruit pulp is derived from the fruit of the baobab tree (*Adansonia digitata*) of the family Bombacaceae. The baobab tree otherwise known as the "upside down tree" produces large green or brownish fruits, which are characteristically iridescent. *A. digitata* grows primarily in South Africa, Botswana, Namibia, Mozambique and Zimbabwe but is also found in India, Sri Lanka, Malaysia, China and Jamaica.

3. PhytoTrade Africa proposes to market baobab dried fruit pulp as a novel food ingredient (NI) for use in a range of food products such as smoothies, cereal bars and other similar food products. The applicant also intends to market a depectinised version of the fruit pulp.

4. PhytoTrade Africa is a trade association that represents individual companies in Africa who would like to export their baobab dried fruit to the EU. PhytoTrade Africa acts as an umbrella organisation and operates a Pre Qualified Supplier (PQS) system which assesses and maintains members' standards to ensure a consistent approach to the production and quality of the product.

5. The information supplied by the applicant highlights that the NI is unprocessed and has a long history of traditional use in Africa. The applicant considers that this history of use provides adequate reassurance about the safety of the product, thereby reducing the need for conventional safety studies which are normally required in a novel food assessment.

6. The application dossier was published on the Agency's website for public consultation and two comments were received. The first suggested that baobab fruit pulp is not a novel ingredient as it is a source of cream of tartar, which is not the case. The second comment related to yeast/moulds and mycotoxins and this point is covered in sections XII and XIII below.

I Specification of the Novel Ingredient (NI)

Information on this aspect is provided on p.1 6 – 9 and 19-27 of the application dossier

7. Baobab dried fruit pulp is obtained from the fruits of the baobab tree (*Adansonia digitata*). The baobab fruit comprises of a very hard outer shell, whitish powdery pulp and kidney shaped seeds. The shell and the seeds are removed and discarded. The pulp is then sieved and stored in the form of a fine powder.

8. In response to questions from the Committee, the applicant provided further information on the procedures employed for the harvesting and processing of the fruit. The physical nature of the fruit (which resembles a coconut in hardness) provides some reassurance that damage leading to possible environmental and microbiological contamination will be minimal.

9. The applicant also submitted additional data which showed the NI to have minimal contamination with soil and other detritus. The level of acid insoluble ash found in one sample was attributed to inappropriate handling and the use of trial production technology. The applicant proposed that this result, which would fall outside the specification of the NI, should be ignored. Another sample appeared to contain a disproportionably high amount of endogenous material (i.e. material other than pulp, derived from the fruit. The applicant noted that this sample was one that had been prepared in under laboratory conditions and may therefore have limited relevance to the commercial product. The applicant highlighted that four other samples had consistently lower levels of endogenous material

10. The applicant has provided details on the phytochemistry of compounds found in the seeds, roots, leaves, bark and fruit of A. *digitata* based on literature reports. According to scientific literature various triterpernoids (beta-sitosterol, beta-amyrin palmitate, alpha-amyrin palmitate and ursalic acid) are present in the fruit. Organic acids such as citric, tartaric, malic, succinic and ascorbic acid have also been reported to be present in the fruit pulp.

11. The applicant also intends to market the NI as a powdered, depectinised extract, as the pectin content of the raw pulp may have an undesirable viscosity and cloudiness which can limit product applications. This product is not considered in detail because pectinases (The applicant intends to use Pectinase 714L, Biocatalysts) are permitted treatments in the preparation of fruit juices (Directive 2001/112/EC), indicating that their use should not give any cause for concern in this application.

12. The applicant has provided nutritional data on three batches of the NI. Each batch is from a different region and has been analysed in duplicate. The results indicate that there is little regional difference in composition of the NI.

13. The vitamin C content of the NI is variable and reported values (4 samples, 3 analysed in duplicate) show a range between 74 and 163 mg per 100g fruit pulp. A number of B vitamins are also present in the NI and the content of thiamine and riboflavin varies between 0.05-0.11 and 0.01-0.03 mg/100g respectively. Analysis's of the amino acid content has also demonstrated that the levels are consistent between geographical locations.

14. The pectin content of the NI varies from 23.4-33.8% by weight, which is consistent with values reported in the scientific literature.

15. The NI contains low levels of fatty acids (less than 1%). The fatty acid composition of the NI as determined by gas chromatography is as follows:

    - Alpha linoleic acid 17-20%
    - Linoleic acid 13-20%
    - Oleic acid 19-31%

16. The applicant also shown that the trace metals present in the NI are comparable with values reported in scientific literature for baobab fruit. Levels of arsenic, cadmium, lead and mercury were found to be within agreed safety levels.

17. As the NI is harvested in the wild it is not anticipated that pesticides will be present in the final NI. However, a multi-residue screen for pesticide content was carried out on three batches of the NI, which confirmed that no residues were detectable.

18. A detailed specification for the NI is attached at Annex A

Discussion: *The Committee was satisfied that the information supplied by the applicant demonstrated that the product was harvested in a manner that ensured that process contamination was kept to a minimum. The Committee also accepted that the data provided by the applicant adequately described the compositional profile of the NI.*

II. Effect of the production process applied to the novel food

Information on this aspect is provided on p.10 of the application dossier

19. A simple, exclusively mechanical, process is used to obtain the fruit pulp. First the fruit is harvested, the hard outer shell of the fruit is cracked and the contents removed. The seeds are then separated from fibrous material and mesocarp. This is screened to remove further unwanted fibrous and flaky material, leaving a fine mesocarp powder, which is stored in clean food grade packaging.

20. The applicant states that during the production process the moisture content falls to around 10 – 13%. Fruit pulp from different areas within a particular region is blended to give a consistent product from one batch to another.

21. In response to a request from the Committee regarding shelf life, the applicant provided additional analytical data to show that the levels of Vitamin C and other key nutrients remained stable over time. The applicant did not indicate a specific shelf life for the products but concluded that these data demonstrate that dried Baobab fruit pulp is stable over the time period examined.

22. Also in response to the Committee's concerns about the rigour of the quality control system, the applicant provided additional clarification as to the extent of the Pre-Qualified Supplier System. The applicant has indicated that regular audits will take place to ensure that the NI produced by their suppliers is within the stated specification (Annex A).

Discussion: *The Committee was satisfied with the applicant's proposed production process and audit procedures.*

III. History of the organism used as the source of the novel food

23. See Section X below.

IX. Anticipated intake/extent of use of the novel ingredient

Information on this aspect is provided on p.13-14 of the application dossier

24. The applicant that Baobab dried fruit pulp and the depectinised pulp should be used in such products as smoothies, at a level of 6-8%, and cereal bars at levels between 5% and 10%. The applicant estimates that intake of the NI would be 6-10g in a 100g smoothie drink, and 10-15g in a 100g cereal bar.

25. The application also refers to potential use in other, unspecified, health food products at levels around 5-10%. The applicant suggests that the pulp could be used in biscuits, confectionery and other (unspecified) related food products.

26. The applicant has not provided any calculations based on dietary survey data and it is therefore not possible to estimate average, and high level intake of the NI arising from consumption of the specified products.

    Discussion: *The Committee was content that the intended uses of the NI did not give rise to concern and there was no requirement to restrict use. (See also section XIII below)*

X. Information from previous human exposure to the novel ingredient

Information on this aspect is provided p. 14-19 and Appendices 7/7a/7b of the application dossier

27. The applicant has highlighted a number of publications indicating that the fruit pulp has a long and extensive history of consumption amongst indigenous Africans. The pulp can be consumed as such, in drinks or used as an ingredient in other foods.

28. The applicant has also provided information on current use in Africa from two questionnaires. The first was completed by nineteen participants at the PhytoTrade Annual General Meeting in May 2006 and confirms literature reports that the fruit pulp is widely consumed in the areas where it is available.

29. The second questionnaire was completed by fifteen experts (nutritionists and botanists from Africa, the EU and the US with knowledge of African diets and food crops. These provide additional evidence of that baobab pulp is a familiar food in various parts of Africa and that there are no known toxicity issues. There is a possibly not unexpected laxative effect if the product is consumed in excess.

30. The applicant has also presented a literature review indicating that the baobab fruit (*A. digitata*) is also consumed in India and other *Adansonia* species have a history of consumption in Australia (Appendix 7b of the application dossier). There are also references to limited sales in the Europe, for exampling in ethnic markets and in food supplements. However, the Food Standards Agency is satisfied that the fruit pulp does not have a significant history of consumption prior to May 1997 and is therefore to be regarded as a novel ingredient.

31. The fruit pulp is sometimes used as a folk remedy and numerous medicinal uses have been reported in the literature. Laboratory studies have indicated that the pulp may have some antipyretic and hepatoprotective effects. Extracts from other parts of the tree (leaves and roots) have antibiotic effects *in vitro*.

    Discussion: *The Committee accepted that the information supplied indicated that the product has an extensive history of traditional consumption in a significant geographical area of Africa. The Committee did not comment on any perceived health benefits that are attributed to the consumption of the NI as this is outside the scope of a novel food assessment.*

XI Nutritional information on the novel food

Information on this aspect is provided on p.19-28 of the application dossier

32. The applicant highlighted that the NI has a range of potential nutritional benefits due to the high levels of ascorbic acid, pectin, linoleic acid and several B vitamins. Although these nutrients are present in relatively high concentrations compared with other foods, the low level of consumption of the NI means that it is unlikely to have a major impact on the nutrient content of the diet. Further information on the composition/ of the NI is presented in section I above.

33. The presence of anti-nutrients in the NI has also been examined (see Section XIII below).

    Discussion: *The Committee accepted that the nutritional profile of the NI, which was consistent with other fruits, did not provide any cause for concern*

XII. Microbiological information on the novel food

Information on this aspect is provided on p.26 of the application dossier

34. The applicant has carried out analyses of three separate batches of the NI. These results confirmed that levels of coliforms, *E. coli*, *S. aureus*, faecal *Streptococci*, *Salmonella* are within acceptable safety limits. The Committee sought clarification of discrepancies in the recorded levels of yeast and mould contamination. Additional information provided by the applicant indicated that typical levels of yeast were <100cfu/g and moulds are within the range 10^2 – $1.4x10^4$ CFU/g. The applicant has advised that these figures are well within the recommended limits for yeasts and moulds in Dried Foods (to be cooked), specified by the Institute of Food Science and Technology (IFST).

    Discussion: *The Committee agreed that the levels of micro-organisms did not give cause for concern. The Committee noted that that whilst the levels of yeast and moulds appeared to be high, the NI complied with recognised limits for this type of contamination[24]. The Committee was also reassured that the product was analysed for mycotoxins (See XIII below), and that the applicant has undertaken to carry out regular audits that will include an investigation of the extent of yeast and mould contamination.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p.26-35 of the application dossier

Literature survey

35. The survey undertaken by the applicant found no mention of any toxic effects with regard to Baobab fruit pulp.

in vivo studies

36. *LD_{50} test in rodents* – the dossier refers to a study from 1994 in which the results of LD_{50} tests on rodents were reported. The test material was from a different source to PhytoTrade's product and was an aqueous extract of freeze-dried pulp, administered intraperitoneally. The resulting LD_{50} was 8000mg/kg. The applicant has estimated that this is equivalent to 746-840g of fruit pulp for a 70kg adult.

[24] Regulation (EC) 2073/2005 defines microbial criteria for foodstuffs, but does not include a specification for levels of yeast and mould. The IFST recommendations are viewed to be a satisfactory alternative and are widely used by industry.

Natural toxins

37. *Cyclopropene fatty acids* – Sterculic and malvalic acids are two cyclopropene fatty acids (CPFAs) that been found in a large number of seed oils from plant families of the order Malvales (Sterculiaceae, Malvaceae, Bombaceae and Tiliaceae). CPFA's inhibit fatty acid metabolising enzymes leading to an accumulation of saturated fats. They are present in the seed oil of baobab but there are no reports of them being found in the fruit pulp. The levels of fatty acids, including malvalic and sterculic acids, were determined by GC-MS in 3 batches of the NI. The method used and the results obtained are detailed in appendix 18 and summarised in Table XIV (page 30) of the dossier. The range of values for malvalic acid were 0.03-0.18 mg/g and for sterculic acid 0.01-0.08 mg/g. The applicant estimates that there is a safety factor of 3000 between the intake associated with adverse effects (in rat studies) and the estimated intake in humans and concludes that there is no cause for concern.

38. *Erucic acid* is undetectable in the NI (detection limit 0.10%).

39. *Alkaloids* – There are historical reports of the occurrence of an alkaloid, adansonin, in the bark of the baobab tree and in other related species. Studies were commissioned by PhytoTrade to attempt to detect alkaloids in baobab fruit pulp using thin layer chromatography, but none were detected (sensitivity (0.001%)).

40. *Ochratoxin* – analysis of the NI for Ochratoxins showed that all samples were below the level of detection. The Committee recommended that the applicant should additionally carry out analyses for aflatoxin, a mycotoxin commonly associated with dried fruit. The applicant carried out the necessary analyses which confirmed that the levels of aflatoxins were within legal limits (see XII above).

41. *Cyanide* – PhytoTrade baobab fruit pulp samples (hydrolysed and aqueous extracts) were analysed for cyanide content (appendix 21 and Table XVII). All samples analysed were below the limit of detection for the method used (5mg/kg).

Other safety-related data

42. The applicant has presented information from the literature regarding related botanical families, such as the Bombaceae; and no toxicity issues were identified. Questions regarding any known toxicity/safety concerns were also included in questionnaires presented to two separate audiences and none were identified (see paragraph 29 above).

Allergenicity

43. No evidence of any allergenic effects in baobab fruit pulp or other genera of the family Malvaceae was found in the published literature. In addition, a study published in 2001 on the irritant effects of baobab fruit pulp on human volunteers is cited as evidence that the fruit pulp is "non-irritant".

    Discussion: *Members noted that the information provided by the applicant was not typical of other novel food applications, which generally include a series of classical toxicological analyses. However in this specific case Members were reassured that the NI was a simple fruit preparation that formed an integral part of the traditional diet in a large geographical area of Africa.*

    Members were reassured that the additional mycotoxin analyses indicated that the NI would not be contaminated by mycotoxins. Members also noted that the hard outer shell would offer protection and ensure that the NI was unlikely to be damaged and contaminated by fungi before harvesting. Members noted that the applicant's PQS system requires that mycotoxin (aflatoxin) analyses are carried out routinely as a check against post-harvest contamination.

    Members noted that there were no reports of allergenicity in the family Malvaceae and on the basis of this information agreed that the NI was unlikely to be a major cause of be allergenicity and that people with existing food allergies were unlikely to suffer cross-reactions after consuming it. However Members did note that, as with other fruits, there was the potential for individuals develop an allergy to proteins in the NI.

Proposed labelling

44. The applicant has stated that the NI will be labelled in accordance with EU food labelling legislation thereby ensuring that consumers are informed of its presence in food products.

    Discussion: *Members accepted that the product would be labelled appropriately.*

Overall Discussion

45. The information supplied by the applicant offers sufficient reassurance that the consumption of the NI does not give rise to any toxicological or allergenic concerns. Members agreed that the absence of extensive toxicological analyses did not give cause for concern because baobab fruit was a staple part of the diet throughout Africa and a retrospective toxicological assessment would have limited value. In coming to this conclusion the Committee wished to draw a distinction between this application and other foods that had previously subject to a novel food assessment that could be viewed to be a regularly consumed outside the EU. In all previous cases there was either a specific safety

concern (eg allergenicity or liver toxicity) or the food was of limited palatability and was consumed essentially as a natural remedy rather than as a staple part of the diet.

46. The microbiological analysis highlighted that the novel ingredient contained significant levels of yeast and mould contamination. Whilst the Committee accepted that the levels were within guidelines for similar dried products, the issue of mycotoxin contamination was identified as being of particular concern. The Committee was reassured by the additional analyses carried out by the applicant that indicated that levels of aflatoxins were within EU limits for dried fruit. Members were also reassured that the applicant would carry out routine quality control tests to ensure that the NI contains demonstrably low level of aflatoxins.

Conclusion

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by PhytoTrade Africa that the range of uses for Baobab Dried Fruit Pulp is acceptable, subject to the applicant's adherence to the proposed specification and the production parameters described above.

July 2007

Annex A

Product Specification for *Adansonia digitata* fruit pulp powder

Description

The dried and milled fruit pulp of *Adansonia digitata*, originating from Southern Africa

Appearance	Fine, white to pinkish-white powder.
Analytical specification:	
Foreign matter	not more than 2%
Loss on drying	not more than 12%
Solubility	Partially soluble in hot and cold water
Ash	[insufficient data – limits will be determined in the light of future production batches]
Heavy metals:	
Lead	less than 5 mg/kg
Cadmium	less than 0.2 mg/kg
Mercury	less than 0.1 mg/kg
Arsenic	less than 3 mg/kg
Microbiological criteria:	
Total aerobic count	less than 100 000 CFU/g
Yeasts and moulds	less than 10 000 CFU/g
Eschericia coli	Absent in 1g
Staphylococcus aureus	Absent in 1g
Salmonella	Absent in 25g

APPENDIX VI

Mr Andreas Klepsch
European Commission
By email

October 2007 Reference: NFU 684

Dear Mr Klepsch,

Initial Opinion: LYCOPENE from *Blakeslea trispora:* Cold water dispersable products

On 28 August 2007, the UK Competent Authority accepted an application from Vitatene for the authorisation of a cold water dispersible formulation of lycopene from the fungus *Blakeslea trispora* as a novel food ingredient, in accordance with Article 4 of regulation (EC) 258/97. This application is essentially an extension of use for the novel lycopene product authorised in 2006 (Commission Decision 2006/721/EC).

The UK Competent Authority is aware of the current consideration of all forms of lycopene by the European Food Safety Authority (EFSA) as part of the ongoing review of food colours. In view of this, the UK requests that an additional assessment is carried out in order to determine whether a cold water dispersible formulation of lycopene from the fungus *Blakeslea trispora* meets the criteria for acceptance of a novel food defined in Article 3(1) of regulation (EC) 258/97. In referring this application to the Commission for further assessment, the UK requests that the conclusions of the ongoing EFSA review will be taken into account in any subsequent authorisation.

The Advisory Committee on Novel Foods and Processes (ACNFP) has reviewed this application and offered no additional comments regarding the safety of this novel food ingredient. The Committee accepted the view of the applicant that this novel ingredient differed only in its formulation when compared with the form which was authorised in 2006. The ACNFP therefore agreed that the cold water dispersible formulation, which uses an EU authorised food additive, did not give rise to any additional cause for concern, and that the only significant difference was that the new formulation enabled the addition of the novel food ingredient into a broader range of foodstuffs. The Committee acknowledged that any concerns that could arise as a result of increased consumption due to the extension of permitted food categories would be covered by the EFSA review.

I am copying this letter to the applicant.

Yours sincerely,

(By e-mail only)

Dr Chris Jones
For the UK Competent Authority

APPENDIX VII

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on substantial Equivalence of Astaxanthin-rich Oleoresin extracted from *Haematococcus pluvialis* considered under Article 5 of the Novel Foods Regulation

Applicant *Cyanotech Corporation*
73-4460 Queen Kaahumanu Highway
102 Kailua-Kona
HI 96740
USA

Responsible person Dr. Gerald R. Cysewski

Introduction

1. A request was submitted by Cyanotech Corporation to the UK Competent Authority in June 2006 for an opinion on equivalence of an astaxanthin-rich oleoresin obtained from the dried algae biomass of *Haematococcus pluvialis* (BioAstin®) to the existing *H. pluvialis* astaxanthin-rich algal meal (Astaxin™) marketed in the EU by Swedish company Astacarotene AB.

2. Astaxanthin is a xanthophyll (oxygenated) carotenoid, which is found in *Haematococcus pluvialis*. This microalgae is part of the diet of fish and crustaceans (e.g. salmon, shrimps) and is responsible for the pink coloration of their flesh, through the ingestion of astaxanthin.

3. Hard gelatine capsules containing the dried biomass of *H. pluvialis* (Astaxin™) have been sold in the EU by the Swedish company Astacarotene AB[25] prior to 1997. It has also been marketing the whole algal product in bulk form to other EU supplement manufacturers under the name of AstaCarox™.

4. This request addresses substantial equivalence according to the five criteria set out in Article 3(4) of regulation (EC) 258/97: composition, nutritional value, metabolism, intended use and level of undesirable substances contained therein.

[25] Astacarotene AB is the new name of the company Astacarotene now owned by Fuji Chemical Industry Co., of Japan.

Evaluation

Composition

5. The algal strain cultivated by the applicant to produce *Haematococcus* algae meal is *Haematococcus pluvialis* Flotow strain Steptoe. This strain, which is also known as H2B, has been maintained in pure laboratory culture following its isolation in the Steptoe watershed of Nevada (USA). The applicant states that although the exact strain of *H. pluvialis* used by Astacarotene AB is a trade secret, the known *H. pluvialis* strains are expected to be comparable phytochemically if cultivated in a similar manner.

6. The oleoresin will be produced in two standardised forms with a 5% and 10% astaxanthin content (BioAstin® SCE5 and BioAstin® SCE10). The applicant produces its oleoresin from dried *H. pluvialis* using a supercritical CO_2 process to remove the lipid fraction, including carotenoids. The applicant indicates that his extraction procedure is similar to the one used by US Nutra[26] for the production of its astaxanthin-rich oleoresin (Zanthin®) which was given a positive opinion from the UK Competent Authority in accordance with Article 3(4) of the novel food regulation, in June 2004[27].

7. The oleoresin is a thick liquid and contains approximately between 8 and 12% astaxanthin. A series of lots of the raw oleoresin are blended in a stainless steel vat to produce a product with a guaranteed minimum 10% astaxanthin (Bioastin® SCE10). High oleic safflower oil is blended with the raw oleoresin to produce a 5% astaxanthin oleoresin (Bioastin® SCE5).

8. The applicant has compared the composition of the oleoresin with the *H. pluvialis* meal source. The applicant is of the view that the fatty acid composition of the two products is similar. The oleoresin with 5% astaxanthin shows a higher level of oleic acid due to the use of high oleic safflower oil in its manufacturing.

9. The applicant has provided compositional data to show that the fatty acid levels and carotenoid composition are similar in their oleoresin, the dried *H. pluvialis* meal from which it is extracted and the existing *H. pluvialis* algal meal marketed by Astacarotene AB (Astaxin™ and AstaCarox™). Whilst there are small differences in the levels of specific fatty acids, the applicant is of the view that this may be due to variability between *H. pluvialis* strains and/or some analytical variability between labs conducting the analyses, and also the extent to which unsaturated fatty acids have been converted to saturated fatty acids within algal cells during cultivation.

[26] US Nutra is now called Valensa, Inc.

[27] UK Competent Authority opinion on substantial equivalence for US Nutra's astaxanthin-rich oleoresin from *H.pluvialis*, see: http://www.food.gov.uk/multimedia/pdfs/astaxanthinfinal.PDF

10. The total astaxanthin content in *H. pluvialis* meal and the astaxanthin rich oleoresins represents 2-4% and 5-11% of the total weight, respectively. As is the case for the existing product, E-astaxanthin is the dominant geometrical isomer in the *H. pluvialis* meal used to produce the oleoresin, with a small amount of 9Z and 13Z astaxanthin isomers.

11. The applicant recommends a one-year shelf life providing the oleoresin is stored in the dark at <8°C. HPLC measurements revealed losses of 5% or less during the first six months of storage. Typically a supplement manufacturer would incorporate the oleoresin into gelatine capsules or beadlets soon after receiving shipment. The applicant has also therefore conducted stability studies on soft gelatine capsules and microencapsulated gelatine tablet-grade beadlets containing the oleoresin, which showed both products were stable at room temperature for nine and ten months.

Discussion: *The Committee was satisfied that the data comparing the oleoresin, its algal meal source and the existing algal meal show that they are similar in composition and that levels of astaxanthin are comparable.*

b) c) Nutritional Value and Metabolism

12. The nutritional value of the oleoresin lies in its carotenoid content, particularly astaxanthin which is a known antioxidant. The applicant highlighted that astaxanthin is an occasional component in the human diet due to its presence in fish and crustaceans. The oleoresin will be an alternative source of astaxanthin and it is not intended to prevent, cure, treat or mitigate any disease or specific condition.

13. The applicant refers to various studies demonstrating the metabolism of astaxanthin. A study by Showalter et al (2004)[28] has suggested a greater bioavailability in mice of esterified astaxanthin, the predominant form present in *Haematococcus*, than free astaxanthin. In a human study by Osterlie et al (2000)[29], astaxanthin was found to be present in all lipoprotein fractions, after ingestion of a meal containing 100 mg of synthetic free astaxanthin. In another human study by Odeberg et al (2003)[30], the oral bioavailability of esterified astaxanthin administered as *Haematococcus* algae meal was shown to be enhanced in human volunteers by the incorporation of the astaxanthin into lipid based formulations, suggesting that dissolution from the matrix and/or incorporation into mixed micelles may limit the rate of bioabsorption.

[28] Showalter *et al* (2004). Plasma appearance and scar tissue accumulation of non-esterified, free astaxanthin in C57BL/6 mice after oral dosing of a disodium disuccinate diester of astaxanthin (Heptax™). Comparative Biochemistry and Physiology Part C 137: 227-236.

[29] Osterlie *et al* (2000). Plasma appearance and distribution of astaxanthin E/Z and R/S isomers in plasma lipoproteins of men after single dose administration of astaxanthin. Journal of Nutritional Biochemistry 11: 482-490

[30] Odeberg, *et al* (2003). Oral Bioavailability of the antioxidant astaxanthin in humans is enhanced by incorporation of lipid based formulations. European Journal of Pharmaceutical Sciences 19: 299-304.

14. In response to a request by the Committee, the applicant provided further information on the proportion of free and esterified astaxanthin present in the oleoresin compared with the algal meal and how different the effectiveness of these two forms of astaxanthin is in the oleoresin. The applicant explained that the *H. pluvialis* meal contains less than 6% free astaxanthin with the remaining present as esters. This is also the case for the existing *Haematococcus* meal (Astaxin™). The applicant presented chromatographic results on the carotenoid fraction of its algal source in its dossier which showed that it contained 70% monoesters of astaxanthin, 10% diesters of astaxanthin and 5% free astaxanthin, with the remainder consisting of beta-carotene, cantaxanthin and lutein. The applicant also provided additional results of HPLC analyses of the existing algal meal and the oleoresin which demonstrated that the ratio of free astaxanthin to total astaxanthin (free and esterified) is similar.

15. Regarding the metabolism of esterified and free astaxanthin, the applicant explained that the consumption of esterified astaxanthin and free astaxanthin results in only free astaxanthin being present in the plasma; however the rate of accumulation in the plasma is slower with astaxanthin esters because hydrolysis of the esters must first take place prior to absorption. The applicant also highlighted that the bioavailability of astaxanthin esters is enhanced when they are formulated into a lipid-based product. The applicant therefore recommends supplement formulators to use a suitable oil carrier for products containing the oleoresin.

Discussion: *The Committee was content with information provided on the nutritional value of the oleoresin. The Committee also accepted the additional information provided by the applicant which indicated that the oleoresin and the existing algal meal contained the same ratio of free and esterified astaxanthin with the latter having a slower metabolic rate.*

Members agreed that the studies provided by the applicant in relation to the efficacy of the novel ingredient were not relevant to the determination of equivalence.

d) Intended Use

16. The applicant intends to market the oleoresin as an ingredient to be used by food supplement manufacturers in hard and soft gelatine capsules and tablets, with an astaxanthin content of no more than 4mg per capsule. This is equivalent to the astaxanthin level found in algal meal food supplements currently found on the EU market such as Astaxin™.

17. The extract will be available at two standardised astaxanthin titers namely: 10% (BioAstin®SCE10) and 5% (BioAstin®SCE5).

Discussion: *The Committee was content that the intended use of the oleoresin as an ingredient in food supplement and the proposed maximum astaxanthin level of 4mg per capsule were equivalent to those of the existing product.*

e) Levels of undesirable substances

18. The applicant stated that the oleoresin complies with strict limits for levels of microbiological and heavy metal contaminants and it is free from chemical pesticides. Analyses of the oleoresin have demonstrated that both its heavy metal and microbial contents are within the stated safety limits.

19. The applicant has compared the levels of heavy metals and microorganims in the oleoresin with those found in the existing *H. pluvialis* meal (AstaCarox™), and also in US Nutra's astaxanthin-rich oleoresin (Zanthin®). The heavy metal levels are similar except for the level of arsenic[31] (1.2 ppm) in the oleoresin, which is higher than that found in Zanthin® (<0.5ppm) and AstaCarox™ (<0.05ppm). The levels of microorganisms present in the oleoresin are similar to those for US §'s oleoresin (Zanthin®).

20. The applicant states that the manufacture of the oleoresin complies with quality control standards. Precautions are taken to assure that the manufacturing procedures do not contribute any contaminants and analyses of the algal culture and the final extracts are performed on a contractual basis. In response to a request from the Committee, the applicant provided additional information on the quality assurance procedures indicating that a HACCP plan was in place which includes checking for contamination of *Haematococcus* cultures at every stage of the production process. Cultures are monitored daily and if contaminated, the pond culture is destroyed and the pond liner is sterilised with hypochlorite.

21. The applicant was asked to provide further information on the culture conditions of *H. pluvialis*, additional data to demonstrate the absence of undesirable contaminants (such as cyanobacteria) in the culture systems (closed culture and and open pond culture) and whether seasonal variations in the levels of other undesirable substances in the open ponds were taken into consideration. The applicant indicated that manufacture takes place in Hawaii, where the climate allows relatively constant culture conditions to be maintained in the open pond culture systems. The culture temperatures are also maintained well below ambient temperature through the use of cold deep-sea water which would reduce the likelihood of cyanobacterial contamination. No cyanobacterial contamination of open culture ponds has ever been observed by the applicant, and due to the low culture temperature, low nutrient concentrations and

[31] There is no EU limit on arsenic. In the UK, the Arsenic in Food Regulations (SI 159 no 831) as amended lay down a general limit of 1 mg/kg for total arsenic in food. This Regulation excludes fish and edible seaweed where arsenic is present naturally.

high *Haematococcus* biomass, the applicant is of the view that this is unlikely to occur. In addition, the applicant is of the view that the physical layout and location of the facility make air- or water-borne contamination by microorganisms unlikely. The applicant also asked an independent laboratory to analyse three batches of the oleoresin and three batches of *Haematococcus* algal meal for cyanobacterial toxins, in particular Anatoxin-a and Cylindrospermopsin using ESI/MS and MS/MS. These analyses confirmed that the levels of Anatoxin-a and Cylindrospermopsin are below the limit of detection (0.2g/l) in both the oleoresin and the *Haematococcus* algal meal.

22. *Haematococcus* algae also contain small quantities of canthaxanthin, a related carotenoid which, when ingested in large doses over a long period of time, may crystallise in the retina. The applicant has reported that these reversible retinal inclusions only develop when the cantaxanthin dose is greater that 0.2 mg/kg body weight/day. However, the applicant considers that the levels of canthaxanthin present in the oleoresin are not of any safety concern as a 70kg individual would have to consume more that 100 capsules containing the oleoresin per day to reach this dose. However whilst no data have been provided to support this calculation the levels of cantaxanthin present is lower than that reported for the previously-approved product from US Nutra.

Discussion: *The Committee was content that the applicant had quality control procedures in place to minimise the risk of contamination of the algal culture and the oleoresin and noted that batches of the oleoresin had been recently tested and found to contain no detectable levels of cyanobacterial toxins. The Committee expressed some concern that water temperature, physical layout and location of the culture facility were considered by the applicant to be the major factors in preventing contamination with other microbes. In view of this the Committee considered that the applicant should implement a regime to ensure that the final product is tested periodically to confirm the effectiveness of the production controls.*

f) Additional information

23. **Labelling:** The applicant intends that the final products will comply with EU legislation for food supplements and provided example labels for the oleoresin.

24. **Safety studies:** The applicant refers to different animal studies to show the safety of the extract. The conclusions from these studies were that the extract exhibits no ill effects on animals. A 4-week human study by Shimada et al (2004)[32] demonstrated that astaxanthin could be consumed safely at dosages of 2-12mg per day with no ill effects.

[32] Shimada et al., (2004). Safety study of astaxanthin consumption in humans. Fujita Health University, Toyoake, Japan. Excerpted from: Premarket notification for a new dietary ingredient: Astaxanthin, extracted from the Haematococcus pluvialis algae. United States Food and Drug Administration, Docket 95S-0316, RPT236. 6pp.

25. The applicant highlights that the oleoresin was approved in the USA and launched in 1999 and is currently marketed for use in dietary supplements in at least 20 other non-EU countries. The applicant indicated that there have been no reports of adverse reactions to any food supplements containing the oleoresin, with a recommended astaxanthin dosage of 2-12g/day, for the past 10 years.

Discussion: *The Committee was content that the applicant will adhere to EU legislation for labelling of food supplements when labelling the oleoresin.*

Conclusion

26. The Committee concluded that Cyanotech Corporation has demonstrated the equivalence of their astaxanthin-rich oleoresin obtained from *H. pluvialis* with the existing astaxanthin-rich *H. Pluvialis* meal according to the criteria set out in Article 3(4) of the Novel Foods Regulation (EC) 258/97. The Committee recommended that the applicant should implement a regime to ensure that the final product is tested periodically to confirm the effectiveness of the production controls in preventing contamination with toxigenic bacteria.

27. This opinion applies solely to the oleoresin as an ingredient to be used by food supplement manufacturers in hard and soft gelatine capsules and tablets, with an astaxanthin content of no more than 4mg per capsule.

28. Therefore, the astaxanthin-rich oleoresin produced by Cyanotech Corporation can be considered to be substantially equivalent to the existing astaxanthin-rich meal produced by Astacarotene AB.

February 2007

APPENDIX VIII

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on substantial Equivalence of Phytosterols considered under Article 5 of the Novel Foods Regulation

Applicant	Lipofoods Calle Issac Peral, 17 Poligon Industrial Cami Ral 08850 Gava Espana
Responsible Person	Laurent Depelley

Introduction

1. A request was submitted by Lipofoods to the UK Competent Authority, in September 2006, for an opinion on the equivalence of their phytosterols with the phytosterols marketed by Archer Daniels Midland (ADM).

2. ADM gained authorisation for the use of its phytosterols through Commission Decision 2004/333/EC. Lipofoods are therefore seeking a view on equivalence for the use of their phytosterol ingredient in the same food categories specified in ADM's authorisation, namely: yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks and cheese type products[33].

3. According to article 3(4) of (EC) 258/97, the notification procedure applies to "foods or food ingredients ... which on the basis of scientific evidence available and generally recognised or on the basis of an opinion delivered by one of the competent bodies ... are substantially equivalent to existing foods or food ingredients regarding their:

- Composition,
- Nutritional value,
- Metabolism,
- Intended use and
- Level of undesirable substances contained therein."

[33] http://eurlex.europa.eu/smartapi/cgi/sga_doc?smartapi!celexapi!prod!CELEXnumdoc&lg=EN&numdoc=32004D0333&model=guichett

Evaluation

Composition

4. The applicant is claiming equivalence to the specification of phytosterols set out in Annex 2 of Commission Decision 2004/333/EC. The phytosterols are extracted from non-genetically modified soya bean seeds. They are manufactured in the same way as the approved phytosterol product marketed by ADM, with the exception that the solvent used is acetone and not heptane. The specification of the product described by the applicant is consistent with that described in Commission Decision 2004/333/EC, as confirmed by analytical data on 5 batches of the product.

   Discussion: *The Committee noted that the composition of Lipofoods phytosterols complied with the specification of phytosterols in Commission Decision 2004/333/EC.*

Nutritional Value and Metabolism

5. Evidence suggests that the nutritional value and metabolism of Lipofoods phytosterol ingredient is expected to be the same as those produced by ADM. The anticipated intake of phytosterols is not likely to be increased as the ingredient is to be used in the same range of products already approved for ADM.

Intended Use

6. The applicant intends the ingredient to be used in yellow fat spreads, salad dressing (including mayonnaise), milk type products such as semi skimmed and skimmed milk products, fermented milk products, such as yoghurt, soya drinks, and cheese. These products are the same as those authorised for ADM phytosterols.

   Discussion: *The Committee was content that the applicant's product is to be consumed at the same level and in the same range of products as the existing product.*

Levels of Undesirable Substances

7. Limited information on the levels of undesirable substances was given in ADM's application. However, Lipofoods have provided data on the levels of a number of classes of potential contaminants including, polycyclic aromatic hydrocarbons (PAH's), dioxins, herbicides and pesticides, heavy metals, organic solvents and aflatoxins. The applicant claims that all contaminants measured are within acceptable levels and in compliance with EU regulations.

   Discussion: *The Committee was content that levels of undesirable substances in this product were not a cause for concern.*

Labelling

8. The applicant states that labelling of the products containing the phytosterols will be in accordance with Commission Regulation (EC) 608/2004 concerning the labelling of foods with added phytosterols.

Additional Information: Toxicology

9. The applicant has given a brief overview of relevant publications looking at the long-term safety of phytosterols. No adverse effects were reported in any of these studies.

Conclusion

10. The Committee is content that the applicant's approach to demonstrating the equivalence of their phytosterols, to be used in conjunction with the existing phytosterol ingredient is consistent with the criteria set out in Article 3(4) of the Novel Food Regulation (EC) 258/97.

11. Therefore phytosterols marketed by Lipofoods can be considered to be substantially equivalent to the existing phytosterol ingredient marketed by ADM.

12. Lipofoods should ensure that the labelling of products containing their phytosterols comply with Commission Regulation (EC) 608/2004 concerning the labelling of foods and added phytosterols.

February 2007

APPENDIX IX

Dr Bjorn Kristianson
Medimush AS
Agern Alle 3
DK 2970
Horsholm
Denmark

3 October 2007 Reference NFU 636

beta-Glucan-Rich Extract from *Lentinus edodes*

Dear Dr Kristianson

On 18 September 2006 you requested an opinion from the Food Standards Agency, as the competent UK assessment body under the novel foods regulation (EC) No 258/97, on the substantial equivalence of a beta-glucan rich extract from *Lentinus edodes* compared with the existing counterpart (dried fruiting bodies of *L. edodes*) in accordance with Article 3(4) of that regulation. I am writing to inform you that we do not accept that substantial equivalence has been established between these two products.

In reaching this conclusion, we have taken advice from the Advisory Committee on Novel Foods and Processes (ACNFP), which discussed your application dossier by postal correspondence and at its meetings in January, March and September 2007. The Committee acknowledged that your product does not appear to present any safety concerns and accepted that the biological similarities described in your application provided sufficient basis for an application for equivalence to be considered. However, Members concluded that the compositional data that you provided showed significant variation between the two products, and you were unable to adequately explain the batch-on-batch variation in your product. On this basis Members were of the view that the information you provided did not provide an adequate basis for them to accept that the two products are equivalent and, noting also that the conditions for growth are entirely different, they concluded that your product could not be considered substantially equivalent to the dried fruiting bodies.

The ACNFP advised that your beta glucan rich extract from L. edodes should not therefore be considered for authorisation under the simplified procedure for novel foods, which applies to products that are substantially equivalent to an existing food. Instead, any authorisation would have to be granted under the standard procedure described in Article 4 of the regulation.

Please let us know if you intend to convert your application for a dossier for assessment under the "full" Article 4 procedure.

Yours sincerely

Dr Chris Jones
ACNFP Secretariat

APPENDIX X

UK Comments on Synthetic Lycopene

First Email to European Commission (8 January 2007)

The UK wishes to object to this application. We have carried out a preliminary assessment of the application and have some concerns regarding particle size. The UK notes that synthetic lycopene is often referred to as the first example of a food ingredient that will be marketed in a nanoparticulate form, and that Lycovit 10% consists of particles <0.5micrometres in diameter. The UK is therefore of the view that this aspect requires additional information to demonstrate that there are no safety concerns.

I will provide you with additional information regarding this objection on 18 January, once our advisory committee has formally discussed this application. If the committee highlights any other concerns during their assessment I will also advise you of them on 18 January.

Second Email to European Commission (23 January 2007)

Following the e-mail of my colleague Chris Jones on 8 January 2006, I have listed below two additional comments from the UK on the synthetic lycopene application from BASF:

- We note that the Joint FAO/WHO Expert Committee on Food Additive (JECFA) assessed the safety of lycopene as a food colour in June 2006 and set an Acceptable Daily Intake of 0-0.5 mg/kg/body weight. This value is 3 to 4 times lower than the proposed estimated intake for BASF synthetic lycopene. We therefore suggest that the toxicological data used by JECFA to set an ADI for lycopene should also be taken into consideration in the assessment of this application.

- The applicant has specified that the levels of related compounds of the synthetic crystalline lycopene should be no more than 9% because this corresponds to the levels of related compounds in the preparations tested in the toxicological studies presented in the dossier. However, in response to a request by the Dutch Competent Authority, the applicant has indicated that the test materials used in the toxicological studies contained approximately 2% of related compounds. We therefore request an explanation on this discrepancy.

As some members of our advisory committee were absent at the meeting on 17 January when they discussed this application, I have asked them to highlight any additional comments they may have and I will forward these to you by 31 January.

[Note: no further comments were forwarded]

APPENDIX XI

Mr Andreas Klepsch
European Commission
By email

19 April 2007 Reference: NFU 620

Dear Mr Klepsch

Application under (EC) 258/97 for Approval of Antarctic Krill Oil

As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Finnish CA for the above product. This was discussed at the Committee's meeting on 22 March.

The UK is unable to agree with the positive opinion of the Finnish CA and concludes that additional information is required before the assessment of the safety of this product can be concluded.

Intake of the novel ingredient

We note that that, by body weight, the highest consumption of the oil will potentially be in children, but no estimates of intake by children have been provided.

The proposed recommended daily intake of the ingredient from foods will be 500mg whereas food supplements will contain 1000mg of the NI. The applicant states that consumption of supplements will be an alternative to consuming foods fortified with the oil, but this does not explain why the levels of intake should be different.

Labelling

The applicant intends to place an advisory statement on food supplements containing krill oil stating that individuals with coagulopathy, or who are on anticoagulant or other medication should speak to their Doctors. However, it would seem necessary to have the same wording on foods containing the oil.

We would also suggest that the product is clearly labelled as being of fish (or animal) origin as the term "krill oil" may be insufficient to show that the product is not suitable for vegetarians.

Allergy

The applicant proposes to label the ingredient with appropriate allergen labelling in accordance with Directive 2003/89/EC. As there is significant overlap between the allergens found in crustaceans and in molluscs we

would recommend using the phrase 'not suitable for people with a shellfish allergy'. Products containing the oil might be consumed by small children, who do not normally consume significant amounts of crustaceans. It might therefore be helpful to have information on the level of allergenic proteins (e.g. tropomycin) in the oil is order to assess the allergenic risk to this population.

Environmental Impact

Antarctic Krill is fished from the wild in the Atlantic section of the Austral-Antarctic Circumpolar Ocean. Although not relevant to the criteria for acceptance of novel foods, we would nevertheless be interested to know the possible environmental impact on stocks of krill that might result from any increase in fishing that will occur to order to produce the novel ingredient.

Regulation 853/2004 laying down specific hygiene rules for food of animal origin

Although the Finnish opinion refers to Regulation (EC) 852/2004, we would like to point out that fish oil will now have to comply also with Annex III of Section VIII on fishery products under Regulation (EC) 853/2004 relating to specific hygiene rules for food of animal origin. Annex III requires that raw materials used in the preparation of fish oil for human consumption must derive from fishery products deemed fit for human consumption, be prepared in an approved establishment or vessel and transported and stored in a hygienic condition.

History of consumption of Krill

The summary of the application, quoted by the Finnish CA, states that the clinical trials are very short and conducted on young and healthy individuals and conclude that 'since krill has already long been consumed as a foodstuff, no new safety issues are likely.' We note that this history of consumption is limited to and we question whether this is therefore sufficient to demonstrate the safety of the oil.

Yours sincerely,

(By email only)

Dr Sandy Lawrie

Novel Foods, Additives and Supplements Division

APPENDIX XII

08 October 2007 Reference: NFU 692

Dear Mr Klepsch

Application under (EC) 258/97 for Approval of Calcium L-methylfolate

As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Irish CA for the above product. This was discussed at the Committee's meeting on 20 September.

The UK agrees with the positive opinion of the Irish CA, that the use of calcium L-methylfolate produced by Merck Eprova AG should be granted authorisation as a novel food ingredient.

The UK would however like to highlight that it is our understanding that the use of the NI in infant formulae and follow-on formulae requires further assessment by EFSA, prior to any authorisation for this use being considered under Directive 2006/141/EC.

Yours sincerely,

(By email only)

Dr Sandy Lawrie

Novel Foods, Additives and Supplements Division

APPENDIX XIII

04 June 2007 Reference: NFU 0677

Dear Mr Klepsch

Application under (EC) 258/97 for Approval of Noni Fruit Puree and Concentrate

As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Belgian CA for the above product. This was discussed at the Committee's meeting on 30 May.

The UK is unable to agree with the positive opinion of the Belgian CA and concludes that additional information is required before the assessment of the safety of this product can be concluded. In particular we would highlight the following:

Intake of the novel ingredient

We note that, by body weight, the highest consumers of many products listed in table 8 will potentially be young children. An assumption seems to have been made that only current consumers of noni juice will buy other foods containing the ingredient, but we question the validity of this assumption as noni is proposed as an ingredient in products such as jellies, yoghurts, ice-creams which children may also consume. In view of this we do not think that the risk assessment can be completed without an estimate of the intake of the ingredients by children.

It is our view that intake estimates for population subgroups should be routinely provided by companies seeking approval for novel foods, when there is a concern that certain groups may be relatively high consumers or otherwise at higher risk than the general population.

We also note that the information provided by the applicant regarding likely intake levels is based on US consumption, which does not necessarily reflect consumption in the EU.

Hepatoxicity

With regard to the issue of high level consumption, from several dietary sources as described above, we note that the applicant has submitted EFSA's recent opinion on the safety of noni juice as evidence of safety of their puree and concentrate. However we would like to point out that the Panel's conclusion that, on the basis of the information available it is unlikely that consumption of noni juice at the observed levels of consumption induces adverse human liver effects, was based on the consumption of noni juice at the currently observed levels of intake. As the noni puree and concentrate will be available in a wide range of foods, the intake levels could be considerably higher than considered in the EFSA opinion and we therefore question whether their conclusion is applicable if the range of products increases. We would therefore request that if approval is given it should be subject to there being sufficient reassurance that increasing the product range, and the likely consumption of a number of the products by children, does not give rise to concerns regarding hepatoxicity.

Yours sincerely,

(By email only)

Dr Sandy Lawrie

Novel Foods, Additives and Supplements Division

APPENDIX XIV

Table 1 List of Noni juice notifications in 2007

Date of notification	Notifier	Product	Opinion prepared by
4 January 2007	Forlive srl	Noni juice	Italy
23 January 2007	Agrolabs	Noni juice	United Kingdom
16 August 2007	Puravitta	Noni juice	Netherland
20 August 2007	Parada	Noni juice	Poland
27 August 2007	Polfit Sp. z.o.o	Noni juice	Poland
15 October 2007	Leap of Faith Farms	Noni Juice	United Kingdom
14 November 2007	Noni de Tahiti Ltd.	Noni Juice	United Kingdom

Table 2 List of Phytosterol notifications in 2007

Date of notification	Notifier	Product	Opinion prepared by
2 January 2007	Láctea Antequerana S.L	Fermented milk type products with added phytosterols	Directly to the Commission (The phytosterols are same as authorised for Teriaka Ltd)
8 January 2007	Uniekaas Nederland B.V.	Fermented milk type products with added phytosterols	Directly to the Commission (The phytosterols are same as authorised for Teriaka Ltd)
9 January 2007	NV Vandemoortele	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat	Directly to the Commission (The phytosterols are provided by Cognis and/ or Cargill)
7 February 2007	Elmilk Sp. z o.o.	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat	Directly to the Commission (The phytosterols are provided by Cognis)
12 February 2007	Nutrition & Santé Italia S.p.A	Fermented milk type products with added phytosterols	Directly to the Commission (The phytosterols are provided by Cognis)

Date of notification	Notifier	Product	Opinion prepared by
16 February 2007	Lipofoods	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat; milk type and fermented milk type products; yoghurt type products; cheese type products, salad dressings and spicy sauces, and rye bread with added phytosterols	United Kingdom
17 April 2007	Bofrost Distributzione Italia S.pA	Milk type products with added phytosterols	Directly to the Commission (The phytosterols are provided by Cognis)
23 April 2007	Linkosuo Oy	Rye bread with added phytosterols	Directly to the Commission (The phytosterols are provided by Forbed Medi-Tech)
14 May 2007	Oy Foodfiles Ltd	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat; milk type and fermented milk type products; yoghurt type products; cheese type products, salad dressings and spicy sauces, and rye bread with added phytosterols	Finland
31 May 2007	Senoble France	Fermented milk type products with added phytosterols	Directly to the Commission (The phytosterols are same as notified by Vitae-Caps SA)

Date of notification	Notifier	Product	Opinion prepared by
4 June 2007	Quesos Forlasa S.A	Cheese type products with added phytosterols	Directly to the Commission (The phytosterols are same as notified by Vitae-Caps SA, Cognis or Lipofoods)
5 June 2007	Lactalis Nestlé Chilled Dairy Co. Ltd	Milk type products with added phytosterols	Directly to the Commission (The phytosterols are provided by Cognis)
27 July 2007	Vivartia S.A	Fermented milk type products with added phytosterols	Directly to the Commission (The phytosterols are same as notified by Vitae-Caps SA)
7 August 2007	Cormon Miloko Factory	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat	Directly to the Commission (The phytosterols are provided by Cognis)
10 August 2007	Karamolegos Bakery & Confectionary	Rye bread with added phytosterols	Directly to the Commission (The phytosterols are provided by Arboris)
6 September 2007	Elbisco S.A.	Rye bread with added phytosterols	Directly to the Commission (The phytosterols are provided by Cognis)
12 November 2007	Hajdúsági Sütödèk Zrt	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat; milk type and fermented milk type products; yoghurt type products; cheese type products, salad dressings and spicy sauces, and rye bread with added phytosterols	Directly to the Commission (The phytosterols are provided by Fenchem Enterprises)

Date of notification	Notifier	Product	Opinion prepared by
3 December 2007	Aarhus Karlshamn Sweden AB	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat; milk type and fermented milk type products; yoghurt type products; cheese type products, salad dressings and spicy sauces, and rye bread with added phytosterols	Finland
11 December 2007	Health Concern BV	Yellow fat spreads as defined by Council Regulation (EC) No. 2991/94, excluding cooking and frying fats and spreads based on butter or other animal fat	Directly to the Commission (The phytosterol is the same as notified by Cognis)

Table 3 List of Argan oil notifications

Date of notification	Notifier	Product	Opinion prepared by
9 July 2007	Oleador	Argan oil	France
29 August 2007	Pojektmanagement Beratung	Argan oil	France
11 September 2007	Argania Gold	Argan oil	France
5 September 2007	Absim France SAS	Argan oil	France
7 September 2007	Frigini's Kaskade	Argan oil	France
9 October 2007	Arganenoel	Argan oil	France
12 October 2007	S.I.R.H SA	Argan oil	France
15 October 2007	Noumidia Caftan International	Argan oil	France
22 October 2007	Alter Eco	Argan oil	France
2 November 2007	Mogador Naturprodukte	Argan oil	France
5 November 2007	Bio Planète	Argan oil	France
17 December 2007	Perle d'Argan	Argan oil	France

APPENDIX XV

Dr Jonathan Latham
Bioscience Resource Project
PO Box 66
Ledbury
HR8 9AE

Email: jrlatham@biosciencesource.org

20 April 2007 NFU

Dear Dr Latham

Transformation induced mutations in transgenic plants

Thank you for your email of 26 February, which provided clarification on two points relating to your recently published review of transformation-induced mutations in GM plants (Wilson et al, 2006: *Biotechnology and Genetic Engineering Reviews* 23; 209-237). This review and the additional information you provided were considered by the ACNFP when it met on 22 March.

The Committee found that this was an interesting and useful review of information about GM plants and agreed that such plants may contain unintended genetic changes. The Committee considered however that this is already taken into account in the current EU approach to the risk assessment of foods derived from GM plants and did not consider that your review revealed any new risk that requires a different approach.

The Committee pointed out that the risk assessments currently carried out in the EU include information on the sequences of the inserted DNA and the flanking regions. The flanking sequences that are examined are not as long as you have proposed, but the risk assessors are able to ask for any additional sequence information that is needed to complete their evaluation.

The Committee agreed that new GM plant varieties may contain DNA changes at loci other than the insertion site and noted that similar changes occur in plants that have not been subjected to techniques of genetic modification. The Committee is unaware of any evidence that random genetic changes in food plants are likely to be a hazard to the health of consumers; indeed, if there were such evidence, it would call into question the safety of all the current methods of plant breeding and the food we currently eat. For example, non-GM plant varieties carrying induced mutations have been widely grown and consumed for several decades and natural mutants are included in conventional breeding programmes. The Committee would therefore not agree with the assumption in your review that any unintended change to plant DNA equates to a risk.

The EU approach to risk assessment of foods from GM plants also includes an assessment of unintended changes, whether resulting from the inserted transgene or from other unintended genetic changes. Methods for identifying a wider range of unintended changes (metabolomics and other -omics techniques) are being developed and may be applied in the future.

In the very unlikely event that a random genetic change were to introduce a hazard in the form of an undetected novel toxin or allergen, this does not inevitably translate into a risk to consumers, as food processing may remove or inactivate the hazardous component.

Finally, you suggested that animal and human studies should be routinely carried out in order to provide assurance of the safety of GM crops. The use of feeding studies is currently being examined by the European Food Safety Authority and we await the outcome of that review.

Yours sincerely

(sent by email)

Dr Sandy Lawrie

Secretary to ACNFP

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