ACNFP

Advisory Committee on Novel Foods and Processes

Annual Report 2005

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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Advisory Committee on Novel Foods and Processes

Annual Report 2005

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Foreword

This is the seventeenth annual report of the ACNFP and the third 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.

The contents of this report once again reflect the number and variety of applications that have been considered by the Committee and the hard work of the Secretariat, whose assistance and support is vital to the effective operation of the Committee. Details on these applications, together with a range of further information on the work of the Committee, can be found on the ACNFP's new website at www.acnfp.gov.uk.

I would also like to take this opportunity to thank my fellow Committee Members for their advice, support and hard work during the year.

Professor Mike Gasson
March 2006

Introduction

This is the seventeenth annual report of the work of the Advisory Committee on Novel Foods and Processes (ACNFP).

In 2005 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 2005 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 2005 are described in section 5 of the report. A cumulative index of topics considered in the ACNFP's annual reports from 1989 to 2005 can be found in Section 12. Hard copies of previous reports can be obtained from the Committee Secretariat (see section 8). 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 Clinoptilolite

This application from Euremica Environmental, seeking authorisation of clinoptilolite as a novel food ingredient was described in the 2004 annual report. During 2005 the applicant indicated that they were unable to provide additional information to address the safety concerns raised by the Committee.

The Committee therefore concluded its evaluation and in view of the concerns raised in 2004 issued a negative opinion for this novel food ingredient.

This opinion was forwarded to the European Commission for consideration by other Member States. A copy of this opinion is attached at Appendix II.

1.2 Isomaltulose

This application from Cargill Cerestar BVBA for the use of isomaltulose in a range of foodstuffs was described in the 2003 and 2004 annual reports. Following a positive vote at the Standing Committee on the Food Chain and Animal Health in February 2005, Commission Decision 2005/457/EC authorising the marketing of isomaltulose was published in the Official Journal on 23 June 2005.[2]

1.3 Juices and nectars with added phytosterols

This application from Coca-Cola s.a was described in the 2004 annual report. Following the Committee's request for additional information, the applicant provided details as to how they would ensure that products containing the novel ingredient would be distinguished from conventional non-fortified counterparts. The applicant also advised that the product would not be marketed in the 250ml single serving containers that the Committee perceived to be attractive to children, and provided additional clarification as to the nature of the particle size of the ingredient.

[2] Official Journal of the European Union No. L160, 23.6.2005, p.28. Available from the EUR-Lex website at:
http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_160/l_16020050623en00280030.pdf

The Committee was content that the additional information supplied by the applicant adequately addressed its concerns and the assessment of the product was completed. The Committee's opinion was submitted to the European Commission as the basis for the UK's initial assessment report on this application (Appendix III).

Some of the other Member States submitted reasoned objections to the UK opinion and the applicant responded to these concerns in 2005.

1.4 Lycopene oleoresin from tomato

This application from Berry Ottaway & Associates Ltd (UK) on behalf of LycoRed (Israel) was described in the 2004 annual report. The applicant was asked to provide additional information to address a number of concerns raised by the Committee. These related to previous human exposure to the oleoresin; the absence of tomatine in the oleoresin; over-consumption of the oleoresin by children as result of it being used in foodstuffs such as ice-cream, cakes or biscuits; the potential transfer of lycopene to breast-fed infants; the significance of the increased lung weights of female rats in the semi-chronic toxicity study; and poor quality protein analysis.

The Committee was content that the additional information supplied by the applicant and the expert advice from an animal pathologist adequately addressed these issues and completed the assessment of this product. The Committee's opinion was submitted to the European Commission as the basis for the UK's initial assessment report on this application (Appendix IV).

Some of the other Member States submitted reasoned objections to the UK opinion and the applicant will respond to these concerns in 2006.

1.5 Phosphated distarch phosphate

The ACNFP was asked to consider an application from National Starch Food Innovation (UK) for the authorisation of phosphated distarch phosphate (PDP) as a novel food ingredient.

PDP is a chemically modified resistant starch type 4 (RS4) derived from high amylose maize starch. The same modified starch is an approved food additive (E1413) used as a thickening agent in products such as gravies and sauces. As this approval applies only to the use of PDP for technological purposes, the use of PDP for nutritional purposes requires assessment in accordance with Regulation (EC) No 258/97. The applicant proposes to use PDP as a source of fibre in a range of bakery products, where it would partially replace ingredients such as flour.

The Committee asked for additional information from the applicant on a number of issues at its September 2005 meeting. This additional information was considered at its November meeting.

The Committee remained of the view that the applicant did not adequately address its concerns on the effects of consumption by "at risk" groups, particularly diabetics and people with irritable bowel syndrome, or the potential for gastrointestinal intolerance in high level consumers. Members also requested fermentability data on the novel ingredient or other similar Type 4 resistant starches. Members continued to be concerned about the high level consumption of PDP by children and requested reassurance that consumption of high amounts would not lead to increased intolerance.

The Committee also raised concerns that the applicant had not responded to concerns regarding allergenicity, and requested that an unambiguous name be used in order that consumers understood the nature and source of the ingredient.

The Committee also considered the marketing of the novel ingredient as a source of dietary fibre and noted that any claims would need to comply with general food labelling legislation.

The applicant's response to the above concerns will be considered by the Committee early in 2006.

1.6 D-Tagatose

The ACNFP was asked to consider an application from Bioresco on behalf of the Danish Company Arla Food Ingredients for the authorisation of the sugar D-tagatose.

D-tagatose is a monosaccharide, an enantiomer of D-fructose (inversion at C-4) which is not commonly found in food, although it is found at low levels in heat-treated dairy products such as sterilised and dried milk. D-tagatose has 75-92% the sweetness of sucrose and behaves like other sugars in terms of hygroscopicity, and stability under low pH and raised temperature. Its principal purpose is as a carbohydrate source and it is "reported" to be non-cariogenic and to act as a prebiotic.

During preliminary discussions with the applicant, the Secretariat noted that the use of D-tagatose in foods could fall within the legal definition of a sweetener, requiring authorisation under food additive legislation rather than the regulation on novel foods. This issue was resolved following discussion with the Commission and other MS. The consensus view was that D-tagatose should be regarded as a novel food ingredient and not as a food additive.

The Committee considered this application at the March and May meetings. Members were content that the safety of the ingredient had been demonstrated by the applicant, but raised some concerns regarding the proposed use of an advisory statement which would appear on certain foods that contain particularly high levels of D-tagatose warning consumers that excessive consumption could result in laxative effects. The applicant proposed that this statement, which is consistent with the advisory statement that appears on products containing polyols, should appear on any foodstuff that contains greater than 15g per serving of D-tagatose.

However, as data for other poorly absorbed compounds such as sorbitol indicate that pre-school children may be more sensitive than adults and older children, Members advised that the advisory statement should be extended to include all soft drinks that contain more than 1% D-tagatose as such products are more likely to be consumed in relatively high quantities by children. The Committee's opinion was submitted to the European Commission as the basis for the UK's initial assessment report on this application (Appendix V).

This opinion was considered by other EU Member States and as no reasoned objections were received, the Food Standards Agency advised the applicant that they could place their product on the market as a novel food ingredient, subject to meeting specified purity criteria and labelling requirements.

2 Substantial equivalence applications submitted to the UK competent authority

2.1 Noni juice: Mi GmbH

The Committee considered a request from Mi GmbH Switzerland and Mi EU Ltd for an opinion on the equivalence of their noni juice to the noni juice product marketed by GSE Vertrieb.

Members considered this application at the March meeting and requested more detailed compositional analyses. The applicant provided these data.

After consideration of the additional data the Committee was satisfied that the applicant had provided enough data to demonstrate equivalence. A copy of the UK opinion on equivalence is attached at Appendix VI. The applicant notified this product to the European Commission on 28 June 2005.

2.2 Phytosterols: DDO processing

At its November meeting, the ACNFP considered a request from the American company DDO Processing on the equivalence of their phytosterols (Nutraphyl™) to be used in yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks and spicy sauces with phytosterols marketed by Forbes Medi-Tech.

Forbes Medi-Tech initially gained authorisation for use of its phytosterols (Reducol™) in milk based beverages in March 2004 under Commission Decision 2004/845/EC. A subsequent authorisation, based on an opinion on substantial equivalence from the Finnish Competent Authority in April 2005, extended the range of Forbes Medi-Tech products to include yellow fat spreads, salad dressings, fermented milk type products, soya drinks, cheese type products, yoghurt type products, spicy sauces and milk based fruit drinks with added phytosterols/phytostanols (see "Notifications submitted to the European Commission" section on page XX).

DDO Processing will produce their phytosterols using a patented process that leads to a slightly higher level of beta-sitosterol (up to 87%) compared to the equivalent manufactured by Forbes Medi-Tech (80%). The total content of phytosterols is similar in the two products (>99%). The Committee indicated that they were satisfied that the proposed upper limit for beta-sitosterol did not rule out consideration of this application under the substantial equivalence procedures. The Committee's consideration of this request will continue in 2006.

2.3 Phytosterols: Prima Pharm

An application was received from Prima Pharm in September 2005 seeking a scientific opinion on the substantial equivalence of their phytosterols with those marketed by Teriaka.

Members noted that Prima Pharm intended to obtain their phytosterols from the French company DRT and details of DRT's tall oil derived phytosterols were contained in the original novel food application from Teriaka. However since gaining approval for all the phytosterols described in their application, Teriaka has not marketed products containing phytosterols manufactured by DRT.

The committee confirmed that they were satisfied that the evidence provided demonstrated the equivalence of the phytosterols to be marketed by Prima Pharm.

A copy of the UK opinion on equivalence is attached at Appendix VII. The applicant must formally notify the European Commission when they first market the product.

3 Applications submitted to other Member States

3.1 Alpha-cyclodextrin

In November 2005, the ACNFP considered an opinion from the Belgian Competent Authority on an application for authorisation of alpha-cyclodextrin as a novel food ingredient.

Alpha-cyclodextrin is a non-reducing cyclic saccharide consisting of six alpha–1,4-linked D-glucopyranosyl units produced by the action of cyclodextrin glucosyltransferase (CGTase) on hydrolysed starch. The applicant intends to market this novel ingredient solely for its nutritional properties as a dietary fibre.

Members were unable to agree with the positive opinion of the Belgian Competent Authority and highlighted a number of issues. These related to the effect of the novel ingredient on diabetics, the consumption estimates provided by the applicant, the potential for high level consumption of the product by children aged between 2-5 years, and the use of the term 'dietary fibre' on the label of products containing the novel ingredient.

The Committee's comments on this application were forwarded to the European Commission in December 2005 (Appendix VIII).

3.2 Arachidonic acid-rich fungal oil

In November 2005, the Committee considered an opinion from the Netherlands' Competent Authority on an application for authorisation of arachidonic acid-rich oil derived from the fungus Mortierella alpina intended for use in infant formula for both premature and full-term babies.

The oil is produced by the fungus *Mortierella* alpina and consists of approximately 41% arachidonic acid, a long chain polyunsaturated fatty acid. The oil also comprises of a number of other fatty acids, each present at levels of up to 10%. Arachidonic acid is currently obtained from other sources including *Mortierella alpina*.

The Committee broadly agreed with the Netherlands' positive opinion and the UK Competent Authority's response is attached at Appendix IX.

3.3 Betaine

This application from Finnfeed Finland Ltd to place betaine on the market as a novel food ingredient was described in the 2003 annual report.

Following reasoned objections raised by the competent authorities in some Member States, including the UK, this application was referred to EFSA in June 2004.

In April 2005, the EFSA Dietetics Nutrition and Allergy Panel published an opinion, which concluded that the safety of betaine for the intended use as proposed by the applicant had not been established.

Following a positive vote at the June 2005 Standing Committee on the Food Chain and Animal Health, Commission Decision 2005/580/EC refusing the placing on the market of betaine as a novel food ingredient was published in the Official Journal on 29 July 2005.[3]

3.4 DHA-rich oil from *Ulkenia* sp.

In May 2005, the ACNFP considered an unfavourable initial opinion from the German Competent Authority regarding an application from Nutrinova to extend the use of DHA-rich algal oil derived from the microalgae Ulkenia sp. The German Competent Authority raised concerns about high level consumption of the oil and concluded that an additional assessment was required.

This application follows the notification sent by Nutrinova to the European Commission in November 2003 for this oil. This notification was sent after obtaining a positive opinion from the German Competent Authority indicating that the oil from *Ulkenia* sp. was equivalent to a similar oil from *Schizochytrium* sp. marketed by Martek. This notification is described in the 2004 Annual Report.

A number of the new food uses proposed by Nutrinova were included in the original Martek application for a similar DHA-rich oil, which was submitted to the UK in 2001. Although Members did not raise any concerns over the inclusion of these additional food categories, they were not included in the list of authorised uses of Martek's product due to concerns raised by competent authorities in other Member States (see 2001, 2002 and 2003 annual reports).

The Committee generally agreed with the initial opinion from the German Competent Authority that an additional assessment was required in order to clarify the issue of high level consumption.

This application, along with Martek's request for similar uses for their algal DHA oil, has been referred to EFSA to determine whether the proposed extension of use increases the risk to consumers.

[3] Official Journal of the European Union No. L199, 29.7.2005, p.89. Available from the EUR-Lex website at http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_199/l_19920050729en00890089.pdf

3.5 GM maize line GA21

This application was described in the 2000, 2001, and 2002 annual reports. The authorisation of products from this maize line was referred to the Council of Ministers during 2005 and authorisation was issued by the European Commission on 13 January 2006.

3.6 GM maize line MON863

This application was described in the 2003 and 2004 annual reports. The authorisation of products from this maize line was referred to the Council of Ministers during 2005 and authorisation was issued by the European Commission on 13 January 2006.

3.7 Isomaltulose

In January 2005, the ACNFP considered a favourable initial opinion from the German Competent Authority for isomaltulose that the applicant (Südzucker AG) proposed to market as a novel food ingredient.

This ingredient is almost identical to the isomaltulose ingredient manufactured by Cargill Cerestar, which was described in the 2003 annual report and subsequently authorised in June 2005.

The Committee generally agreed with the initial opinion from the German Competent Authority but expressed reservations about labelling and emphasised their previous concern that the use of isomaltulose could result in an overall increase in energy intake due to misinterpretation of any claims made for reduced sweetness or delayed energy release. These comments were forwarded to the European Commission on 28 January 2005 (Appendix X).

Following a positive vote at the June 2005 Standing Committee on the Food Chain and Animal Health, European Commission Decision 2005/581/EC authorising the marketing of isomaltulose was published in the Official Journal on 29 July 2005.[4]

3.8 Plant sterol enriched rice drink

In March 2005, the ACNFP considered a favourable initial opinion from the Finnish Competent Authority regarding an application for authorisation of a plant sterol enriched rice drink as a novel food.

[4] Official Journal of the European Union No. L199, 29.7.2005, p.90. Available from the EUR-Lex website at:
http://europa.eu.int/eur-lex/lex/LexUriServ/site/en/oj/2005/l_199/l_19920050729en00900091.pdf

The Committee generally agreed with the Finnish Competent Authority provided that the labelling of this product is in accordance with Regulation (EC) 608/2004. Members also commented on the proposed labelling and drew attention to the absence of efficacy data directly attributing the lowering of blood cholesterol to the consumption of this product.

The Committee's comments were forwarded to the European Commission on 31 March 2005 (Appendix XI). Following reasoned objections raised by other Member States, this application has been referred to EFSA.

3.9 Zeaxanthin

In September 2005, the ACNFP considered an unfavourable initial opinion from the Dutch Competent Authority on an application for the authorisation of Zeaxanthin as a novel food ingredient.

Zeaxanthin is a fat-soluble xanthophyll pigment that is naturally present in some fruit and vegetables. Zeaxanthin and the closely related pigment lutein are the most common xanthophylls naturally present in such foods.

The Committee agreed with the Dutch Competent Authority that an assessment cannot be completed without information relating to the intended uses.

The Committee raised a number of concerns which they felt should also be considered in an additional assessment. These related to the stability of the novel food ingredient, the effect of consuming zeaxanthin as a food supplement on "at risk" groups such as the elderly and high-end users and implications of consuming zeaxanthin for the high user group.

The Committee's comments on this application were forwarded to the European Commission on 13 October 2005 (Appendix XII).

As the principal concern raised by Member States relates to risk management, rather than risk assessment, the Commission will decide whether this application should be referred to EFSA, after further consultation with the applicant and Member States.

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".

4.1 Noni juice

During 2005, the European Commission has distributed a total of 10 notifications from companies for the marketing of noni juice considered to meet the criteria for substantial equivalence with another product that is already on the EU market. The table at Appendix XIII provides details regarding these notifications:

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.

Since June 2004, the Commission has distributed a total of 30 notifications from companies for the marketing of phytosterol fortified products considered to meet the criteria for substantial equivalence as these notifications raise no new issues, they have been brought to the Committee's attention but not discussed. All the companies who have notified their products in the EU under this simplified procedure are listed in the table at Appendix XIV. For completeness this table includes notifications made during 2004.

5 Other issues considered by the ACNFP

5.1 Codex Intergovernmental Task Force on Foods Derived from Biotechnology

In August the Committee was asked to consider the proposed work programme of this recently re-formed Codex Task Force. Comments were particularly sought on the relative importance of the projects proposed by the European Commission and any significant uncertainties in the science that might limit the success of the proposed projects within the allotted timescale.

Members considered that the proposed activities were sensible and were generally content with the prioritisation of the issues. However, it was suggested that food safety issues specific to staple food crops for developing countries could be given a higher priority, and that the issues related to GM plants expressing pharmaceutical or other bioactive substances could be addressed through the provision of guidance on biopharming. In relation to the latter, it was further noted that minimising the risk to consumers from accidental contamination of the food supply with bioactive plant products was a crop segregation and traceability issue, rather than a scientific one.

The Committee welcomed the inclusion of a proposal related to the safety assessment of GM hybrids but highlighted the absence of any proposal examining possible improvements to the methodologies of the current safety tests. Members also noted that the definition of "modern biotechnology" used by Codex excludes cloning and tissue culture, although these techniques are also of interest.

The Committee noted that there was considerable commercial interest in the modification of non-food plants for the production of pharmaceuticals and other substances. Such systems, involving contained growth facilities, are subject to different regulatory controls than GM crops intended for food and feed. Techniques, such as transient expression systems, are also being developed in this area and may fall outside the current definition of biotechnology.

While the Committee suggested that it was unlikely that all of the proposed issues could be tackled within the allotted 4-year timeframe, Members did not identify any significant uncertainties that might limit the success of any individual projects.

The Committee was later informed that the Codex Task Force met on 19-23 September and agreed to establish two initial projects, on the safety assessment of GM animals and on nutritionally modified GM crops. The latter would include crops of importance to developing countries. These project proposals are subject to formal endorsement at the next meeting of the Codex Alimentarius Commission, which oversees the work of all the Codex Committees and Task Forces.

5.2 Effect of GM soya on newborn rats

In November the Committee was asked to consider a report provided by Dr Irina Ermakova which contained the results of a preliminary study conducted in Russia on the offspring of rats which had been fed genetically modified soya beans. The results indicated that the offspring of the rats given the GM soya flour had reduced growth and increased mortality compared to the control groups.

Members found the study to be inconclusive as it lacked essential detailed information about the composition of the test materials. The Committee indicated that there were a number of possible explanations for the results of this study aside from the origin of the test materials. The Committee also noted that the study had not been quality-controlled by the peer-review process for scientific publications.

Additionally, the Committee drew attention to the fact that the study's conclusions were not consistent with those described in a peer-reviewed paper published in 2004.[5] This paper reported the results of a well-controlled study in which mice were fed on diets containing 21% GM herbicide-resistant soya beans and followed through up to 4 generations. This study did not show any adverse effect of the GM soya.

The Committee indicated that it would consider any further information that could be obtained and that it will review the position if a full report of the study is published in the peer-reviewed literature.

The Committee issued a statement on 5 December 2005, a copy of which can be found at Appendix XV.

5.3 EFSA GMO Panel safety assessment of GM maize hybrids

At the September meeting the Committee was asked to consider the EFSA GMO Panel opinions on an earlier application for authorisation of grain and grain-derived food ingredients from 3 maize hybrid lines, MON863 x NK603, MON863 x MON 810 and MON863 x MON810 x NK603, under Regulation (EC) No 1829/2003.

[5] "A generational study of glyphosate-tolerant soybeans on mouse fetal, postnatal, pubertal and adult testicular development" Brake DG and Evenson DP; Food and Chemical Toxicology 42 (2004) 29-36.

In July 2004 Members had considered the EFSA GMO Panel opinion on an earlier application for authorisation of food ingredients derived from MON863 x MON810 maize hybrids in the context of an earlier application under the novel foods regulation. At that time the Committee had some concerns, primarily based on the fact that these were the first GM hybrids to be evaluated by EFSA. The Committee advised that it was necessary to consider the potential for interactions in hybrid plants and noted that this evaluation would set a precedent for future hybrid dossiers (see 2004 Annual Report).

EFSA had since adopted its "guidelines for the risk assessment of GM plants and derived food and feed" which considers these general questions. The Committee was therefore asked if it agreed with the GMO Panel's opinions and in particular the strategy used to assess the safety of hybrids, given its previous comments. The Committee confirmed that it agreed with the GMO Panel opinions.

5.4 EFSA guidance document for the risk assessment of genetically modified microorganisms and their derived products intended for food and feed use

EFSA issued an open consultation on its guidance document for the risk assessment of genetically modified microorganisms (GMMs) on 15 July. The Committee was invited to provide comments for inclusion in the UK's response to this consultation at the September meeting.

The Committee provided comments on a number of aspects of the guidelines including the transfer of antibiotic resistance markers, allergenicity, and the methods used to kill or remove live GMMs from final products. These comments, together with those from the Advisory Committee on Releases to the Environment (ACRE), were incorporated into the UK response to the consultation that can be found at Appendix XVI.

5.5 Food use of GM maize line 1507

The Committee had previously considered an initial opinion under Regulation (EC) 258/97 from the Netherlands Competent Authority for maize 1507, an insect and herbicide resistant GM maize line (Annual Report 2004). As the UK and some other member states had raised reasoned objections, the application could not be completed under the novel foods regulation and was transferred to Regulation (EC) No 1829/2003 on GM food and feed, which came into force in April 2004.

In March 2005 the Committee considered the EFSA opinion on this maize line which included responses to the concerns raised previously by

Member States. The Committee was satisfied with the applicant's response concerning the specificity of expression of novel genetic material and assessment of the allergenicity of novel proteins that might be present, but requested sight of several documents submitted to EFSA that were not part of the original dossier. These were reviewed at the May meeting and there were no further concerns.

5.6 GM food safety assessment

The Committee commented on points raised in a letter received from Genetic Food Alert after the November 2004 open meeting, which centred on the safety assessment of foods derived from GM sources.

The letter raised a number of questions concerning research into the safety of foods derived from GM sources using feeding trials on animals and humans. The Committee stated that feeding trials represent an important tool in certain specific circumstances but confirmed that there is no scientific justification for insisting that all novel (including GM) foods should be subject to routine feeding trials. The Chairman's reply to this letter can be found at Appendix XVII.

5.7 Nanoparticles in food

The Committee was asked to comment on relevant issues related to nanoparticles in food and identify aspects that may require further discussion following the publication of a Royal Society and Royal Academy of Engineering report entitled 'Nanoscience and Nanotechnologies: Opportunities and Uncertainties'[6] and a follow up response by the Government.

The Committee agreed that the use of nanoparticles in food was an issue of increasing public interest that would require further consideration and emphasised the importance of developing a dialogue on the subject. Members also indicated that the Committee might require input from additional experts if it is to examine this area in depth.

[6] The full report is available at http://www.nanotec.org.uk/finalReport.htm.

5.8 Structure and immunogenicity of bean alpha-amylase inhibitor expressed in peas

The Committee was asked to comment on a paper[7] that details immunological effects in mice exposed to peas genetically modified to contain the bean protein alpha-amylase inhibitor-1 which confers resistance to the pea weevil. These results indicated that the protein expressed in transgenic peas has a different structure and different immunological properties compared with the native protein that is present in beans.

Members considered that the post-translational modification of proteins was not a new phenomenon and is assessed as a part of the safety assessment of GM foods. This illustrated the importance of using plant-derived proteins in the safety assessment rather than a microbial equivalent. No risk was identified for this GM pea line and it was noted that the immunological effects were not allergenic ones.

[7] Prescott VE et al. Transgenic Expression of Bean Alpha-Amylase Inhibitor in Peas Results in Altered Structure and Immunogenicity, Journal of Agricultural and Food Chemistry 53; 9023-9030 (2005)

6 Developments elsewhere

6.1 Review of the novel foods regulation

There was no further progress during 2005 and discussions on revisions to the regulation are expected to begin in 2006.

6.2 GM food and feed regulation

During 2005 the Committee were updated on the status of applications for authorisation under Regulation (EC) No 1829/2003 on GM food and feed. As of 1 November, there had been 22 applications, including five for individual GM maize events, nine applications for maize hybrids and four applications for GM cotton lines/hybrids. Other applications were for GM rice, sugar beet, potato and soya bean. The GM potato had been altered to enhance amylopectin production. The other applications were for events which conferred either herbicide tolerance or insecticide resistance, or both.

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:

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8 References

1. Advisory Committee on Novel Foods and Processes. Annual Report 1989. Department of Health and Ministry of Agriculture, Fisheries and Food, 1990 (Available from the ACNFP Secretariat).

2. Advisory Committee on Novel Foods and Processes. Annual Report 1990. Department of Health and Ministry of Agriculture, Fisheries and Food, 1991 (Available from the ACNFP Secretariat).

3. Advisory Committee on Novel Foods and Processes. Annual Report 1991. Department of Health and Ministry of Agriculture, Fisheries and Food, 1992 (Available from the ACNFP Secretariat).

4. Advisory Committee on Novel Foods and Processes. Annual Report 1992. Department of Health and Ministry of Agriculture, Fisheries and Food, 1993 (Available from the ACNFP Secretariat).

5. Advisory Committee on Novel Foods and Processes. Annual Report 1993. Department of Health and Ministry of Agriculture, Fisheries and Food, 1994 (Available from the ACNFP Secretariat).

6. Advisory Committee on Novel Foods and Processes. Annual Report 1994. Department of Health and Ministry of Agriculture, Fisheries and Food, 1995 (Available from the ACNFP Secretariat).

7. Advisory Committee on Novel Foods and Processes. Annual Report 1995. Department of Health and Ministry of Agriculture, Fisheries and Food, 1996 (Available from the ACNFP Secretariat).

8. Advisory Committee on Novel Foods and Processes. Annual Report 1996. Department of Health and Ministry of Agriculture, Fisheries and Food 1997 (Available from the ACNFP Secretariat).

9. Advisory Committee on Novel Foods and Processes. Annual Report 1997. Department of Health and Ministry of Agriculture, Fisheries and Food 1998 (Available from the ACNFP Secretariat).

10. Advisory Committee on Novel Foods and Processes. Annual Report 1998. Department of Health and Ministry of Agriculture, Fisheries and Food 1999 (Available from ACNFP Secretariat).

11. Advisory Committee on Novel Foods and Processes. Annual Report 1999. Department of Health and Ministry of Agriculture, Fisheries and Food 2000 (Available from the ACNFP Secretariat).

12. Advisory Committee on Novel Foods and Processes. Annual Report 2000. Food Standards Agency 2001 – FSA/0013/0301 (Available from the ACNFP Secretariat).

13. Advisory Committee on Novel Foods and Processes. Annual Report 2001. Food Standards Agency 2002 – FSA/0553/0302 (Available from the ACNFP Secretariat).

14. Advisory Committee on Novel Foods and Processes. Annual Report 2002. Food Standards Agency 2003 – FSA/0824/0403 (Available from the ACNFP Secretariat).

15. Advisory Committee on Novel Foods and Processes. Annual Report 2003. Food Standards Agency 2004 – FSA/0919/0604 (Available from the ACNFP Secretariat).

16. Advisory Committee on Novel Foods and Processes. Annual Report 2004. Food Standards Agency 2005 – FSA/0983/0505 (Available from the ACNFP Secretariat).

Electronic versions of the annual reports listed above are also available on the ACNFP website at:
www.acnfp.gov.uk

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 35).

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 2004, 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 2004 can be found on page 24.

A copy of the code of conduct for ACNFP members can be found on page 28.

Membership of the Committee during 2005

Chairman

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

Members

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

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

Dr Hilary Close BSc, PhD, PG Dip (Consumer Representative)
Member of the Science and Technology Committee of the National Council of Women of Great Britain.

Neville Craddock MA, CSci, FIFST (Food Processing and Quality Assurance Expert)
Non-Executive Director of Law Laboratories Ltd and Independent Consultant.

Professor James Dunwell BA, MA, PhD (Plant Biotechnologist)
Professor of Plant Biotechnology, School of Biological Sciences, University of Reading.

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

Dr John Fowler BVM&S, PhD, FATS, CBiol, FIBiol, FRCPath, FRCVS (Toxicologist)
Independent consultant and registered toxicologist with experience in pharmacology and pathology.

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.

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

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

Dr Clive Meredith BA, MA, MSc, PhD (Toxicologist/Immunologist)
Head of Immunology at BIBRA International Ltd.

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

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

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

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 2005

	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
Professor R Chadwick	Glaxo Smithkline	Occasional consultant	Food Ethics Council	Member
			ESRC	Research Funding
			Eursafe	Member of Executive Committee
			Wellcome Trust	Research Funding
			MRC	Member of Advisory Council on Scientific Advances in Genetics
Dr H Close	None	None	None	None
Mr N Craddock	Various	Consultant on short-term projects	None	None
Professor J Dunwell	None	None on short-term projects	BBSRC/EU	Research Funding
			Biohybrids	Studentship
Professor M Gasson (Chairman)	Novacta Biosystems Ltd	Shareholder	Various	IFR Food Safety Science Division industry-funded research projects
Professor G Foster	BBSRC RAE Institute Assessment Exercise Science Panel	Member	BBSRC/DEFRA/DfID/Gatsby	Research Funding
	BSPP/Blackwells Molecular Plant Pathology	Editor-in-Chief	Horticultural Research International Central Science Laboratories	Research Funding (PhD student support)
	Adjucation Panel for Science & Technology R&D funding in Ireland	Panel Member	British Society of Plant Pathology	Member
	Biotech/Molecular/Biomedical Enterprise Ireland	Panel Member	Molecular Biotechnology	Editorial Board

ACNFP Members' interests during 2005 *(continued)*

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
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 Synairgen Southampton Asset Management	Consultant Shareholder/Director Director	Novartis MSD Wyeth Avantec Various charities and trusts	Research Funding Trustee
Dr P Lund	None	None	BBSRC Leverhulme Trust Darwin Trust Food Ethics Council	Departmental Research Director
Professor A Malcolm	None	None	None	None
Dr C Meredith	None	None	Various	Departmental Commissioned Research

ACNFP Members' interests during 2004 *(continued)*

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
Professor I Rowland	Alpro foundation Glanbia Clasado Halifax Woolwich	Consultant Shareholder	Vitacress Geest Cerestar (Belgium) Yakult UK Alpro Nicobrand	Funded Research PhD Studentships
Professor P Shewry	Journal of Cereal Science Various Various Biochemical Society Society for Experimental Biology Phytochemical Society American Association of Cereal Chemists Institute of Biology	Reviews editor Occasional laboratory review panel member Editorial Member Fellow	Defra link programmes NIAB	Funded Research Trustee and Board Member

ACNFP Members' interests during 2004 *(continued)*

	Personal Interests		Non-personal Interests	
Member	**Company**	**Interest**	**Company**	**Interest**
Dr A Williams	None	None	Rank Prize Funds Children Nationwide 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 Women & Children First (charity organisation)	Sponsorship of college course Provision of un-paid advice. 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 32);

- 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;

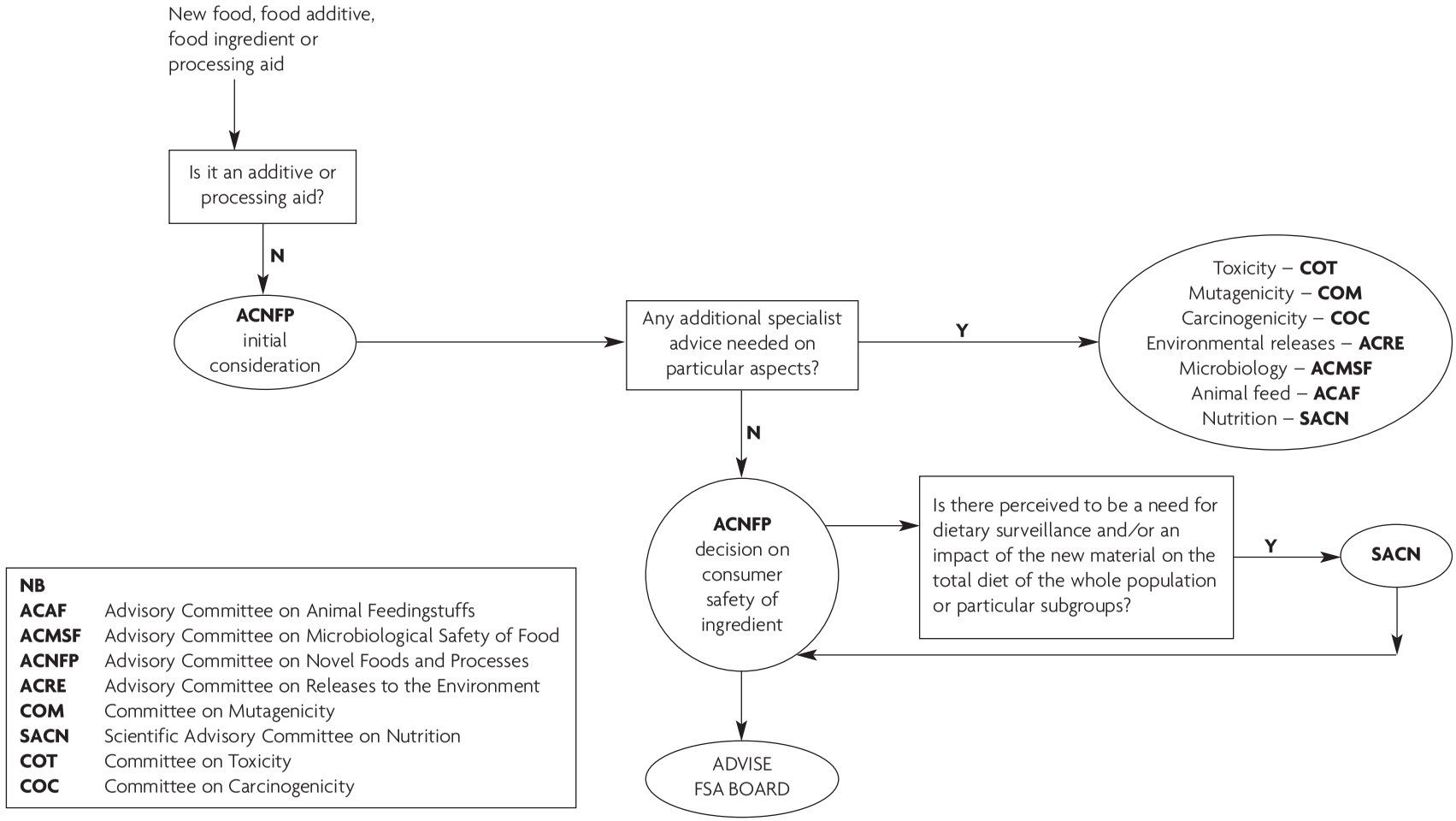
- Trade associations representing companies involved with such products;

- 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.

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

Opinion on an application under the novel foods Regulation for Clinoptilolite as a food ingredient

Applicant	Euremica Environmental Ltd
Responsible person	Mr Rob Sampson
EC Classification	2.2

Introduction

1. An application has been submitted by Euremica Environmental Ltd. for authorisation of clinoptilolite as a novel food ingredient to be used as a food supplement in the EU, on 5 January 2004. A copy of this application dossier was placed on the Food Standards Agency web-site for public consultation and no comments were received.

2. Clinoptilolite is the geological term for a naturally occurring zeolite aluminosilicate mineral. Clinoptilolite is formed by the devitrification (the conversion of glassy material to crystalline material) of volcanic ash in lake and marine waters millions of years ago. As with other zeolites, clinoptilolite has a cage-like structure consisting of SiO4 and AlO4 tetrahedra joined by shared oxygen atoms. The negative charges of the AlO4 units are balanced by the presence of exchangeable cations – notably calcium, magnesium, sodium, potassium and iron. These ions can be readily displaced by other substances, for example heavy metals and ammonium ions. This phenomenon is known as cation exchange and is the major property of clinoptilolite to be utilised by the applicant. The applicant wishes to market clinoptilolite as a dietary supplement intended to carry out this ion-exchange process in the GI tract thus helping to remove commonly consumed heavy metals such as lead and cadmium from the body.

3. The Medicines and Healthcare products Regulatory Agency were consulted on the status of this product and they were of the view that clinoptilolite is not a medicinal product.

4. Several mineral-derived products are currently permitted in foods in the EU. Many of these are silicate minerals, such as calcium silicate, talc and kaolin that are widely used as additives in the processing of cheese, including pre-packed grated cheese.

5. The application for the authorisation of clinoptilolite 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 placing on the market of novel foods and novel food ingredients. Clinoptilolite has been classified as a complex novel food ingredient from a non-GM source (class 2.2). This opinion presents the information provided in the dossiers under the schemes outlined in the Commission Recommendation which was considered by the ACNFP in February 2004, but it does not investigate or comment on the perceived nutritional effects that the applicant attributes to the consumption of clinoptilolite.

I. Specification of the novel food

Information on this aspect is provided in the application dossier, p. 6-13

6. Euremica Environmental Ltd. proposes to market clinoptilolite as a novel food ingredient (NI) in food supplements, which will be sold in capsule form. It is proposed that each capsule will contain 250mg of clinoptilolite and 340g of rice flour together with the anticaking agents magnesium stearate (E470b) – 6mg and silicon dioxide (E551) – 6mg. The NI has an approximate empirical formula $(Ca,Fe,K,Mg,Na)_{3\text{-}6}Si_{30}Al6O_{72}.24H_2O$ and CAS number 12173-10-3.

7. Deposits of clinoptilolite can be found throughout the world. The applicant has stated that their NI will be obtained from a single mine in Queensland, Australia. According to the applicant, this deposit is of very high purity and contains very low levels of lead. In addition the applicant proposed to analyse each batch to check the composition. Any batch found to contain an unacceptable level of any element likely to cause harm would be rejected and not used for human consumption.

8. Most elements will be quantified using Inductively Coupled Plasma Mass Spectrometry (ICP-MS). This method is not suitable for elements such as silicon, sulphur and the halogens and these elements will be quantified using other methods, which are described in detail in the dossier, (page 10). Should the applicant be obliged to source their product from another mine, the same stringent tests and safety procedures will be used.

9. Five samples from one batch of clinoptilolite were analysed for elemental content (Table 1 of the dossier, pages 7-9). The low levels of heavy metals in the product suggest that consumers will be are well below the Provisional Tolerable Weekly Intake levels as set by JECFA[8]. The applicant notes that this analysis assumes that all the heavy metals present in clinoptilolite are totally absorbed in the GI tract whereas in reality only low levels of these metals are likely to be solubilised and absorbed through the gut wall.

[8] **JECFA:** the Joint FAO/WHO Expert Committee on Food Additivies

10. The applicant stated that they will screen each batch of product before encapsulation for heavy metal content, dioxins, micro-organisms and protein to ensure that the product does not exceed acceptable levels for these impurities. The applicant however, has not indicated what the acceptable levels might be.

    Discussion: *The Committee noted that the production process for the NI was basic and raised some concerns over the high silicon content of the NI, which could induce crystalluria in people who are susceptible to renal calculi, and concluded that there was insufficient information regarding the levels of impurities.*

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

Information on this aspect is provided in the application dossier, p. 13

11. The NI is obtained from Supersorb Environmental NL, who are owners of a mine in Duaringa, Queensland, Australia. The NI is removed from the mine using a bulldozer and transferred to the crushing and screening plant. The rock is crushed and milled to achieve a particle size of 30-50 microns. The clinoptilolite is then bagged and shipped to the UK.

12. The supplement capsules will be manufactured within an approved facility in accordance with Good Manufacturing Practice (GMP) guidelines.

13. The applicant has stated that the production process will not confer any adverse toxicological or microbiological properties to the product. However, as a precaution, the applicant will heat their product to above 100°C to kill any micro-organisms or denature any protein as outlined in section XII. The Applicant will also test each batch for a variety of impurities as outlined in section I.

    Discussion: *Members considered the proposed heat treatment of the NI to 100°C was insufficient to ensure denaturation of the protein and requested characterisation of the protein present in the NI in order to evaluate potential allergenicity.*

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

Information on this aspect is provided in the application dossier p. 14

14. The applicant has not supplied information under this heading, noting that clinoptilolite is a mineral. However, the dossier describes previous human exposure to clinoptilolite outside of the EU. As far as the applicant is aware, no adverse effects have been noted from this exposure (Section X).

15. Clinoptilolite is currently used within the EU in drinking water purification, although not in the UK. Clinoptilolite from volcanic and sedimentary sources is authorised in the EU for use as a binder, emulsifier or thickener in animal food for pigs, poultry and rabbits.

Discussion: *Members noted the information provided by the applicant.*

IV. Anticipated intake/extent of use of the novel food ingredient
Information on this aspect is provided in the application dossier p 21-27

16. The applicant intends to use the NI only as a dietary supplement and is not seeking to incorporate the product into any other foodstuffs. The availability of this product will not be restricted geographically and there are no plans to target the product at specific sectors of the public. Based on its established ability to bind heavy metals, the applicant anticipates that the NI will also be purchased by companies who handle toxic and/or radioactive metals or by hospitals and/or public authorities who may wish to stock the NI in case of possible contamination by radioactive materials.

17. The dosage will be four capsules per day, two in the morning and two in the evening; the equivalent of one gram of clinoptilolite per day.

Discussion: *The Committee noted that the proposed use of clinoptilolite was limited to supplements but considered that the information provided by the applicant on the human consumption of the NI provided insufficient reassurance that the proposed levels of consumption would not be harmful.*

V. Information from previous human exposure to the novel food ingredient or its source
Information on this aspect is provided in the application dossier, p 17-18

18. The applicant has not provided any information pertaining to the sale of dietary supplements containing the NI outside the EU but has supplied details of medicinal products containing clinoptilolite consumed in other parts of the world. In Bulgaria pills and biscuits were prepared for human consumption with added clinoptilolite to help absorb heavy metal radioisotopes present in food after the Chernobyl disaster.

19. Clinoptilolite has also been approved by the Cuban Drug Control Agency as an anti-diarrhoeic drug. The Cuban drug is called Enterex and consists of purified natural clinoptilolite. The applicant has outlined four clinical trials carried out for the Cuban Drug Control Agency. These trials included a dose determination trial and a study consisting of 73 volunteers with acute diarrhoea who were given a

dose of 2-6 tablets each containing 900 mg of clinoptilolite every 4 hours. The final two studies involved treatment of over 400 diarrhoea patients with Enterex. No adverse effects of clinoptilolite were demonstrated and no drug interactions were found between Enterex and Tetracycline, Chloramphenicol, Metronidazole and Sulphamethoxazole. A low level of adsorption of aspirin, theophylline, propanolol and phenobarbital was demonstrated. The applicant has not investigated the effect of this product on the efficacy of these drugs but the labelling suggestion they have provided includes a warning about consumption of clinoptilolite when taking medication.

Discussion: *The Committee considered the information relating to previous human consumption of clinoptilolite as a medicine to be supporting data only, as these uses fall outside the scope of the Novel Foods Regulation (EC) 258/97.*

VI. Nutritional information on the novel food ingredient

Information on this aspect is provided in the application dossier p. 19-22

20. The applicant wishes to utilise the purported ion exchange, heavy metal and mycotoxin binding properties of the NI and have provided studies that they believe demonstrate the adsorption of mycotoxins and heavy metals by clinoptilolite and their subsequent removal from the body.

21. Clinoptilolite has been found to bind only weakly to the essential micronutrients copper, zinc, cobalt and manganese. The applicant is of the opinion that the aluminium present in the product will only be poorly absorbed into the bloodstream, as the product will mostly pass through the body unaltered except for the ion-exchange process.

Discussion: *Members did not comment on the proposed functionality of the NI as this is outside the scope of (EC) Regulation 258/97. Members were also concerned that the product might affect the absorption and activity of some medicines, nutrients (such as beta-carotene) and gut hormones and requested further data in these areas. Finally, Members would like to see more human studies carried out on the product, in particular to address concerns that the product may remove essential trace elements from the gut. This effect would not be evident in animal studies, as these use standard diets supplemented with trace elements that may be present only at low levels in the human diet.*

VII. Microbiological information on the novel food ingredient

Information on this aspect is provided in the application dossier, p.23

22. Clinoptilolite is an aluminosilicate mineral of volcanic origin, which contains a very low water content and would not be expected to harbour bacterial contamination. The applicant has tested two samples of the NI for microbiological safety and has found that E. coli, S. aureus and Salmonella were undetectable in both samples. The aerobic colony count and yeast were ‹10 cfu/g and mould count was 100 cfu/g for one sample and ‹10 cfu/g for the other. Certificates for the microbiological analysis of the clinoptilolite samples have been provided. As stated in the dossier (page 12), the applicant intends to heat the product to temperatures ›100°C before encapsulation to ensure that any micro-organisms present will be killed.

    Discussion: *Members considered that the proposed heat treatment may not be sufficient to kill bacterial spores that may be present in the NI and asked for analyses to be carried out to demonstrate that these were absent from the NI.*

VIII. Toxicological information on the novel food ingredient

Information on this aspect is provided in the application dossier, p.24-25

23. The applicant has provided details of several toxicology studies carried out using clinoptilolite. Apart from the studies on cation exchange, these studies were carried out on clinoptilolite from other producers.

Exchangeable Cations

24. To demonstrate the low level of exchangeable cations present in the product the applicant has included an in vitro study which uses ammonium ions, for which clinoptilolite has a very high affinity, to give the maximal exchange. The table below shows the results obtained for those metals that were present in measurable quantities.

Element	Total quantity in clinoptilolite (% or ppm)	Proportion of element exchanged after exposure to ammonium ions (%)
Sodium	0.39%	50%
Magnesium	0.69%	10%
Aluminium	4.3%	0%
Calcium	2.0%	43%
Titanium	0.21%	0.7%
Manganese	520ppm	0.5%
Strontium	0.11%	35%
Yttrium	32ppm	2.3%
Barium	0.18%	24%
Lanthanum	38ppm	1.8%
Praseodymium	14ppm	3.8%
Neodymium	45ppm	4.3%

25. The table above indicates that elements which are present within the body such as sodium, magnesium and calcium will be most likely to undergo ion exchange within the GI tract and be deposited into the gut whereas only very low levels of metals such as yttrium and lanthanum will be exchanged and deposited within the gut. Levels of exchangeable zinc, cadmium, lead, nickel and copper were below the limit of detection.

Gastric Fluid Extractable Elements

26. A further *in vitro* experiment was carried out using synthetic gastric fluid to quantify key elements that are particularly extractable from the NI in the human stomach. Five replicates were analysed and the results are shown in the table below.

Element	Concentration in gastric fluid on completion of study (mean ∓ SD)	% extraction *
Antimony	Not detected	–
Mercury	Not detected	–
Cadmium	0.5 ± 0.31ppb	13.9
Chromium	4.1 ± 0.9ppb	2.5
Arsenic	12.5 ± 0.28ppb	15.6
Copper	19.5 ± 6.1ppb	7.0
Nickel	20.6 ∓ 1.0ppb	64.4
Cobalt	21.8 ± 0.6ppb	34.1
Titanium	62.5 ± 1.7ppb	0.1
Lead	91.8 ± 8.1ppb	14.8
Zinc	164.7 ± 5.8ppb	15.0
Phosphorus	4.4 ± 0.2ppm	70.0
Silicon	20.2 ± 0.6ppm	0.4
Manganese	4.6 ± 0.1ppm	44.2
Barium	3.7 ± 0.4ppm	10.3
Strontium	5.6 ± 0.2ppm	25.5
Iron	7.4 ± 0.3ppm	2.7
Potassium	6.8 ± 1.0ppm	3.1
Magnesium	30.5 ± 1.0ppm	22.1
Aluminium	147 ± 5.0ppm	17.1
Calcium	158 ffl 4.0ppm	39.5

* calculated from the total of each element in the sample, based on previous analysis

27. The table above indicates the levels of elements detectable in the synthetic gastric fluid solution after incubation at 38° for 2 hours. Elements commonly utilised by the body such as calcium, manganese and phosphorus are shown to dissolve in the gastric fluid solution more readily than elements which are not used in the body such as titanium. The table also shows the proportion of the total of each element that has been dissolved in the gastric fluid solution.

Acute, Subchronic and Chronic Toxicology Studies

28. Three studies were performed by Pavelic *et al* (2001): an acute toxicity study (1 month), a sub-chronic toxicity study (3 months) and a chronic toxicity study (6 months). Mice fed 25% clinoptilolite were monitored daily for phenotypic changes, behavioural changes and survival. Body weight changes were monitored on a weekly basis. Food and water consumption levels were checked twice during the study. Haematological and serum clinical chemistry parameters were tested after 1, 3 and 6 months and urine clinical chemistry parameters were tested after each month. Pathohistological analyses were carried out on liver, spleen, kidney, brain, lung, testes, ovary, duodenum, eye, stomach, large and small intestine, muscles, myocardium, pancreas, thymus and axillary lymph node. No statistically significant changes were observed for any of these 3 tests.

29. Pavelic also carried out a similar study on Wistar rats using a variable ratio of cliniptilolite in their diet. The rats were monitored daily, over periods of 1, 3, and 6 months, for phenotypic changes and changes in food consumption, behaviour and survival and every four days were monitored for changes in body weight and water consumption. Changes in haematological and serum clinical chemistry parameters were tested once a month and pathohistological analysis of liver, spleen, lung, kidney, testes, ovaries, and brain were performed at necropsy. No statistically significant changes were noted for any of these parameters.

Carcinogenicity

30. Carcinogenicity of respirable clinoptilolite particles (5mm) has been investigated in Wistar rats administered intratracheally with single doses of 0, 30 or 60 mg. None of the experimental groups showed a significant increase in the incidence of any specific tumours compared to the corresponding control groups and no positive trend was noted in the occurrence of tumours. Anatomical sites and histopathological characteristics of tumours were similar in control and test groups. The authors of the study were of the opinion that clinoptilolite has no carcinogenic activity in rats when administered intratracheally.

Reproductive and Developmental Toxicity

31. Three separate reproductive toxicity tests have been carried out using a diet of clinoptilolite administered in the diet of rats, mice and pigs.

32. Pond and Yen (1983) concluded that the addition of clinoptilolite to the rat diet at 5% had no apparent adverse effect on growth or reproduction. No evidence of toxicity or teratogenicity was found and the offspring grew normally and reproduced normally.

33. Pavelic *et al* (2001) reported on a study using a diet containing 25% clinoptilolite given for 50 days (males) and at least 14 days (females) before mating. The animals and their offstring were observed through 4 reproductive cycles (4-5 months). The test group had increased litter sizes, which the authors considered was responsible for observed changes in the offspring, which had a reduced gain in body weight until weaning and the higher mortality between days 8 and 21. The authors concluded that there were no adverse effects on reproduction that were attributable to clinoptilolite administration.

34. A reproductive toxicity study (Kyriakis *et al* 2002) was carried out on pigs given a diet containing 2% clinoptilolite. No adverse effects were noted in the sows of the experimental group and they showed normal oestrus behaviour during the breeding period. The sows had a slightly improved farrowing rate when compared to the control group. No teratogenic effects were reported.

35. Kyriakis *et al* carried out a further study on crossbred sows fed a diet containing 2% clinoptilolite. This study was carried out for a complete reproductive cycle and a number of serum parameters (P, K, Cu, Zn and vitamins A and E) were monitored. The authors of the study were of the opinion that the administration of clinoptilolite did not significantly change the levels of these parameters, with the exception of a reduction in the levels of vitamin E.

Repeated Dose Dermal Toxicity

36. In a study from Pavelic et al (2001) clinoptilolite was applied to the skin of male Wistar rats and male BALB/c mice either as a powder, a mixed neutral cream in a ratio of 1:1 or mixed with paraffin oil at a ratio of 1:1. No dermal toxicity or allergenicity was observed.

Animal Nutrition Applications

37. Several studies have been carried out in animals to investigate agricultural uses for clinoptilolite. The studies suggest that the addition of clinoptilolite to the diets of poultry, pigs and ruminants helps to improve weight gain and feed conversion as well as milk yields. Incidence of scours, enteritis and other intestinal diseases also seemed to be reduced in the test groups when compared to the control groups. No obvious adverse effects were noted and no necropsy was carried out.

38. The applicant has also provided studies that they believe demonstrate that the addition of clinoptilolite into the diet helps to protect the animals from the effects of mycotoxins such as aflatoxins, which are thought to bind to the clinoptilolite and are subsequently excreted from the body. The authors of these studies state that addition of clinoptilolite to animal feed has resulted in measurable improvements in the health of pigs, sheep and chickens.

Zeolite A: Toxicology Studies.

39. The applicant has provided data that relates to zeolite A, a type of synthetic zeolite very similar in structure to clinoptilolite and has many uses in household detergents. No developmental or carcinogenic effects have been observed during studies with zeolite A.

Discussion: *Members noted that the available toxicity studies on clinoptilolite products did not indicate any adverse effects but highlighted that these were primarily acute studies, often with non-oral administration. However, it is anticipated that the NI will be consumed as a dietary supplement on a chronic basis and the Committee considered that the information provided did not provide sufficient reassurance of safety.*

The Committee noted that the majority of studies did not provide information relating to particle sizes of the test materials, but some such as those conducted by Pavelic et al (2001) indicated that the particle size ranged from 1-3µm. The Committee considered that further information was needed to confirm the relevance of these studies to the NI, which has a particle size of 30-50 microns

Also, a paper by Martin-Kleiner et al (2001)[9], not mentioned in the application dossier, reported on the effects of clinoptilolite on hematopoiesis and serum chemistry in mice given 12.5% or 25% in the diet (uniformed particle sizes with an average diameter of 2.68µm). The animals were studied at 10-day intervals up to 40 days and the authors observed leukocytosis accompanied by bone marrow changes in the treated animals. This effect was attributed to intestinal irritation and inflammation elicited by rough zeolite particles and was less marked when clinoptilolite was administered in a more finely powdered form. The significance of these findings for the clinoptilolite preparation described by the applicant should be determined.

Labelling

40. The applicant has indicated that the label will state the following:

"Zeolife®, part of the Euremica Environmental range, is a natural supplement that contains micronised zeolite. Taken regularly as part of a balanced diet, it helps to maintain a healthy body.

Ingredients Rice Flour, Zeolite, Capsule Shell (Gelatine, Water), Magnesium Stearate, Silicon Dioxide.

[9] Martin-Kleiner I, Flegar-Mestric Z, Zadro R, Breljak D, Stanovic Janda S, Stojkovic R, Marusic M, Radacic M, Boranic M. The effect of the zeolite clinoptilolite on serum chemical and hematopoiesis in mice. Food Chemistry Toxicology 39 (2001) 717-727

Warning if you are pregnant, nursing, taking medication or have a medical condition, consult your doctor before taking this product. Discontinue use if you notice any unusual effects. KEEP OUT OF REACH OF CHILDREN

Directions for use Swallow four capsules per day with liquid, two in the morning and two in the evening. This container provides 30 days' supply. DO NOT EXCEED THE RECOMMENDED DAILY INTAKE"

Discussion: *The Committee also requested that applicant should either indicate a dose on the label for children or recommend that the product is not suitable for consumption for this population group. Members also noted that advisory warning should be placed on the packaging to address the concerns regarding silicon consumption by individuals who are susceptible to renal calculi (see para 10 Discussion above).*

Overall discussion

41. The risk assessment for the use of clinoptilolite in food supplements cannot be completed, as the information provided by applicant does not offer sufficient reassurance of safety. In particular, the applicant would need to provide additional data to address the concerns highlighted in this opinion.

Conclusion

42. The Advisory Committee on Novel Foods and Processes has concluded that, the safety data provided by Euremica Environmental for the approval of clinoptilolite as a novel food ingredient are inadequate and does not support the approval of this novel food ingredient in accordance with Regulation (EC) 258/97.

December 2005

APPENDIX III

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on an application under the novel foods Regulation for drinks consisting of fruit juices or nectars with added phytosterols

Applicant: Coca Cola Services S.A.
Responsible Person: Dr Michael Knowles
EC Classification: 2.1

Introduction

1. An application has been submitted by Coca-Cola Services s.a. for the authorisation of fruit juices (including tomato juice) and fruit nectars with added phytosterols as novel foods (NF).

2. This is the first full novel food application made for phytosterol fortified foods since the entry into force of the labelling regulation, (EC) 608/2004. Regulation (EC) 608/2004 sets out measures to reduce the likelihood of the over-consumption of plant sterols. The regulation also requires that at risk groups, who should avoid the consumption of these ingredients be clearly identified by means of clear labelling.

3. This application differs from previous applications for foodstuffs with added phytosterols by virtue of the intended food types. Previous applications have involved foods that contain significant amounts of fat, which facilitates the incorporation of phytosterols. In this case the applicant uses phytosterols in the form of micro-sized particles that can be more readily incorporated into fruit juice and fruit nectars, which are largely fat-free.

I. Specification of the novel food
Information on this aspect is provided on pp 2-4 of the application dossier

4. The proposed NF will consist of fruit juices or fruit nectars[10] with added phytosterols at a maximum level of 0.4%. The proposed NF will contain no more than three portions and a 250ml portion of NF will contain up to 1g of phytosterol.

5. There are limits on the designation 'fruit juice' when other ingredients are added. Council Directive 2001/112/EC of 20

[10] Fruit nectar is a product made by combining fruit juice with water and may have added sugar and/or honey and/or sweeteners. Nectars are not widely available in the UK.

December 2001 relating to fruit juices and similar products intended for human consumption does not allow products consisting of fruit juice with added phytosterols to be described as a "juice". The general specification for the named fruit will also comply with the recommendation made by the Association of the Industry of Juices and Nectars from Fruit and Vegetables of the EU (AIJN).

6. The phytosterol ingredient is supplied by Cargill Inc, who have recently gained a positive opinion on the equivalence of their ingredient compared with that produced by Pharmaconsult. This opinion, issued in August 2004 by the Finnish Competent Authority (CA), permits the use of Cargill's phytosterol ingredient in a number of specified foodstuffs, namely yellow fat spreads, spicy sauces, milk and fermented milk drinks. The intention to market this ingredient in a range of products (which did not include fruit juice) was notified to the Commission in November 2004.

7. The applicant has provided analytical results to show that the manufacturing method results in a concentration of phytosterols in the final product that consistently meets the specifications.

8. The applicant has also evaluated the stability of the phytosterol ingredient in orange juice using one batch containing 1.12g of total phytosterols. These data showed that the phytosterol content in orange juice is stable and unaffected by the manufacturing process or a 9-week storage period.

Discussion *Members were satisfied with the specification of the novel food.*

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

Information on this aspect is provided on pp 5 – 6 of the application dossier

Production of juices and nectars

9. The juices and nectars (without phytosterols) are currently produced by the applicant in accordance with current EU processing and hygiene legislation and comply with established HACCP procedures. The same processes will apply to products with added phytosterols.

Production of phytosterol ingredient

10. The phytosterol ingredient is derived from tall oil soap, a by-product of wood processing, which is subject to two-stage distillation. The production process has been evaluated by the Finnish CA and they have concluded that the ingredient is equivalent to existing phytosterol ingredients that have been assessed for safety and authorised under the novel foods regulation (see above).

Production of the NF

11. The applicant will add the phytosterols to concentrated juice or nectar in the form of micro size particles with an average size of 0.01mm, which will be verified by particle size analysis. The mixture will be processed to completely disperse the phytosterols. This mixture will then be blended with water and added vitamins.

12. The final product, or 'juice-based-drink', will be packed in a uniquely shaped container providing 3 servings of 250-330ml. The label will indicate the name of the NF as "orange juice drink with added plant sterols" and the list of ingredients will include "orange juice from concentrate (99.6%); plant sterols (0.4%)".

    Discussion *Members were satisfied with the additional assurance from the applicant that the 'micro-sized' phytosterol particles to be used in the final product are of a size that does not give rise to any safety concerns. Members were also reassured by the applicants' intention to market the product in a uniquely shaped package that would reduce the risk of accidental purchase due to confusion with existing juices and nectars, and consequent consumption of the ingredient by 'at-risk' groups.*

III. History of the source organism

Information on this aspect is provided on p6 of the application dossier

13. The phytosterol ingredient used by the applicant is derived from tall oil obtained from wood of pine trees, as supplied by Cargill Ltd. Following the positive opinion on equivalence obtained from the Finnish Competent Authority this ingredient has been notified as a novel food ingredient and can be sold in a limited range of foods throughout the EU (see above). Similar phytosterols extracted from tall oil have previously been authorised as novel ingredients.

    Discussion *Members had no concerns over the source of the novel ingredient, which had previously been authorised under the novel food regulation.*

IV. Anticipated intake/extent of use

Information on this aspect is provided on pp 7-14 of the application dossier

14. The mean population consumption of fruit juice and nectars for adults (including consumers and non-consumers) in the UK is 50g/day (97.5th%tile 150g/day). Intakes are similar in other EU countries with the exception of Germany, where it is significantly higher (mean of 111g/day; Dossier p11). In the UK consumption levels among actual consumers of fruit juice are 100 g/day (mean) and 300 g/day (97.5th percentile), which would be equivalent to an intake of 0.4 and 1.2g/day of phytosterols if these consumers replaced existing juices with the phytosterol-containing product.

15. These products are intended to be consumed only by adult individuals who wish to lower their blood cholesterol level and will be labelled to comply with regulation (EC) 608/2004 which sets a maximum phytosterol intake of 3g/day (Dossier p 8-9). Coca-Cola will recommend consumers to drink the NF with meals as follows:

    (a) 2 servings[11] (2x 250 ml) per day, morning and evening, if they are using the NF as their sole source of phytosterol or

    (b) 1 serving (250 ml) per day, if they are already obtaining 1 or 2 servings of phytosterol from other sources.

16. The applicant states that the NF may be more attractive to consumers than yellow fat spreads or dairy products with added phytosterols, especially for consumers who might be lactose-intolerant, and it provides a source of phytosterols that is lower in fat than the existing products (Dossier p 12-13).

17. The applicant is of the view that intake of phytosterols resulting from consumption of the NF, combined with other foods with added phytosterols, will not exceed the recommended limit of 3g/day.

18. As previously noted, the ingredient to be used by the applicant has already been authorised on the basis of an opinion on equivalence, in accordance with articles 3(4) and 5 of the novel foods regulation. If authorised, all products described in the current application will be labelled as required by (EC) 608/2004, including advice on the maximum recommended phytosterol intake and on maintaining adequate carotenoid intake.

    Discussion *Members accepted that the measures described by the applicant would help to ensure that regular consumption of this product will be confined to the target group and that consumers will not exceed the levels recommended by the Scientific Committee on Food in 2003, provided that consumers read and respect the labelling advice. Although pricing is ultimately a commercial decision by the manufacturers and retailers, it is expected that the phytosterol-containing products will be significantly more expensive than existing juices and nectars (as is currently the case for spreads and other products with added phytosterols) which would also tend to limit consumption by non-target groups.*

V. Information on Previous Exposure

Information on this aspect is provided on pp 14-15 of the application dossier

[11] Consuming 250 ml of NF containing 0.4% of added phytosterols is equivalent to consuming 1g of phytosterols.

19. Yellow fat spreads with added phytostanol esters have been consumed in Finland, since 1996 and in the period 1996-2004, over 50 other products have been placed on the market in the EU. Such products are mainly, but not exclusively, dairy based.

20. Following the submission of applications for approval of foods with added plant sterols under the novel foods regulation, the SCF also produced a report in March 2003 reviewing the intakes of phytosterols and phytostanols and specifying specifies the compositional profile of plant sterol ingredients.

Discussion *Members agreed that the proposed sterol mixture had a profile that is in compliance with that specified by the SCF and there are now a relatively large number of products on the market containing equivalent phytosterol mixtures. The Committee agreed that there is no evidence of any concerns related directly, or indirectly to their consumption provided this does not exceed the levels recommended by the SCF.*

VI. Nutritional Information

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

21. The applicant states that the proposed juice drinks and nectars will only contain a small proportion of added phytosterols (up to 0.4%) and the nutritional content of the drink will not differ significantly from conventional juices and nectars. It is also anticipated that consumers could potentially substitute normal juice and nectars with the NF, in which case there should be no impact on overall nutrient intake.

22. The applicant has supplied data to show that consumption of added phytosterols in orange juice decreases total cholesterol by 7.2% and lowers LDL cholesterol by 12.4% when adults drink 240ml of orange juice, containing 1.15g of phytosterols, with their normal meal at breakfast and dinner.

23. Studies relating to the cholesterol lowering efficacy of free, non-esterified phytosterols in low and fat-free foods has been extensively reviewed by Cargill Inc. (Dossier p 18-19). This review concludes that free phytosterols, including fine particle phytosterols are equally effective as phytosterol esters in lowering blood cholesterol. In response to questions from the Committee, the applicant also provided details of additional studies that demonstrate that the size of particles described in the application does not affect the biological properties of the phytosterols.

Discussion *Members agreed that the proposed addition of phytosterols would have no significant impact on the nutritional quality of the fruit juices and nectars, and therefore caused no*

nutritional concerns. The Committee agreed that the use of fine particle plant sterols is equally effective as free and esterified plant sterols in reducing LDL-cholesterol. Members also noted that it is generally recognised that consumption of plant sterols can interfere with the absorption of fat soluble vitamins and that this applies equally to the phytosterol preparation described in this application for use in juices and nectars. Members noted that it was therefore essential that, as is the case for all existing foods containing added plant sterols, consumption of the NF does not cause consumers to exceed the recommended maximum intake of 3g per day of sterols, and that the NF is not regularly consumed by "at risk" groups such as children and pregnant or lactating women.

VII. Microbiological Information

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

24. The applicant states that micro-organisms or their metabolites are not present in the ingredient or would not be present in the final products following the addition of phytosterol novel ingredient. This is supported by the information produced by Cargill in their substantial equivalence dossier.

25. The applicant has stated that the production of juices and nectars with added phytosterols is adequately controlled throughout in order to ensure its microbiological safety.

Discussion *Members agreed that the addition of the phytosterol mixture would not increase the risk of microbial contamination.*

VIII Toxicological Aspects

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

26. The safety of plant sterols in foods has been reviewed by the SCF between April 2000 and April 2003. The applicant is of the view that the proposed addition to fruit juices and nectars does not give rise to any additional concerns.

Discussion *Members agreed that the safety of plant sterols has previously been demonstrated and that the ingredient that the applicant intends to use has been shown to be equivalent to phytosterol mixtures whose safety has previously been assessed in accordance with regulation (EC) 258/97.*

Overall discussion

27. The applicant has provided a reasoned argument as to why the consumption of the novel foods will not increase the risk of over-consumption of phytosterols amongst the target population. The applicant has also indicated that they intend to market the products in distinctive packaging to minimise the risk of at-risk groups

accidentally consuming the products in place of similar, non-fortified drinks.

28. This application does not address the toxicology, microbial safety and allergenicity issues related to phytosterols in detail because the ingredient they intend to use has previously been authorised under regulation (EC) 258/97. This assessment is not altered by the fact that the phytosterol ingredient is to be added to juices and nectars in a microparticulate form.

29. The products described in this application will comply with EU labelling requirements, including regulation (EC) 608/2004 (phytosterol labelling) and Directive 2001/112/EC (fruit juices and similar products). Compliance will ensure that consumers are informed of the nature of the product, which will be clearly marked to show that it contains phytosterols and is not suitable for consumption by "at-risk" groups. The labelling will also indicate that the products should be consumed as part of a healthy diet and that individuals should not consume more that the recommended daily amounts.

30. Members noted the applicant's intention to market juices and nectars as alternative sources of phytosterols for consumers who do not wish regularly to consume existing products such as spreads and dairy-based products. However, the Committee considered that, compared with the existing products, there may be an increased risk of consumption of phytosterol-containing fruit juices by non-target groups who do not need to reduce their cholesterol level but may nevertheless be attracted to this product. In this regard the Committee considered that the applicant's intention to market the product in a distinctive packaging would reduce the possibility of confusion between products with and without added phytosterols. The Committee repeated its earlier advice that the overall intake of phytosterols should be monitored to confirm whether consumption is largely limited to the target group and that consumers do not regularly exceed the recommended maximum intake of 3g per day.

Conclusion

31. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by Coca-Cola Services SA that Drinks consisting of Fruit Juices and Nectars with added Phytosterols are acceptable, subject to the applicant's adherence to the proposed specification and the production parameters described above. The Committee notes that these products will need to comply with the same labelling rules as other phytosterol-containing foods and recommends that the juice and nectar products should be marketed in a distinctive packaging that reduces the possibility of confusion with conventional juices and nectars. To minimise potential consumption by children, the products should not be marketed in single serving packs.

12th April 2005

APPENDIX IV

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on an application under the novel foods regulation for lycopene-rich oleoresin from tomato as a food ingredient

Applicant LycoRed
Responsible Person Peter Berry Ottaway
Novel Food ingredient Lycopene-rich oleoresin from tomato

EC Classification 2.1

Introduction

1. An application was submitted by Berry Ottaway & Associates Ltd (UK) on behalf of LycoRed (Israel) for the authorisation of a lycopene-rich oleoresin derived from tomato as a novel food ingredient (Lyc-O-Mato®), on 7 September 2004. A copy of the application dossier was placed on the FSA web-site for public consultation.

2. Lycopene is a carotenoid with antioxidant properties. Carotenoids are lipid-soluble photosynthetic pigments, which are made up of isoprene units. The term "oleoresin" describes a naturally occurring mixture of a resin and an essential oil obtained from certain plants. LycoRed describes "tomato oleoresin" as a natural extract of tomato lipids which contains various important phytonutrients dissolved and dispersed in its natural oil.

3. LycoRed seeks approval to market its lycopene-rich oleoresin as an ingredient in a range of food products. The same extract is currently used in the EU in food supplements at a dose of 5-15mg of lycopene, which is equivalent to 83-250mg of Lyc-o-Mato 6%. The lycopene extract is also used in more concentrated form as a food colour (E160d). Council Directive 94/36/EC[12] permits the use of the extract as a colour in a range of foodstuffs at levels up to 500mg/kg (expressed as lycopene) but this approval does not extend to the use of lycopene as a food ingredient. The use of the extract as a source of lycopene in food products is therefore subject to the terms and conditions of the Novel Foods Regulation (EC) 258/97.

[12] European Parliament and Council Directive 94/36/EC of 30 June 1994 on colours for use in foodstuffs, Official Journal L 237 , 10/09/1994 p.13 -29

4. The application for authorisation of this oleoresin 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 lycopene-rich oleoresin has been classified as a complex novel food ingredient from non-GM source having a history of consumption in the Community (class 2.1). The information presented in the dossier is structured and considered below, under the schemes outlined in this Commission Recommendation.

I. Specification of the novel food
Application dossier p.6-18

5. The novel food ingredient (NI) consists of a lycopene-rich oleoresin produced from the pulp of ripe tomatoes, also called "LycoRed LRT". These are a non-GM, hybrid variety of tomatoes (Lycopersicon lycopersicum L. Karst. ex Farw) which have been naturally selected for their high lycopene content (150-220ppm).

6. The NI consists of lycopene (5-15%) together with a number of other constituents that occur naturally in tomato. These are fatty acids and acylglycerols (69-74%), unsaponifiable matter (14-19%), water soluble matter (2.7-4.7%), water (0.48-0.86%), phosphorus compounds (0.35-0.52%), phospholipids (8.9-14%), nitrogen (0.16-0.31) and ash (0.7-0.8%). The active ingredient of the NI is lycopene consisting of 90-95% (all-trans)-lycopene. Cis isomers are also likely to be present at small quantities in a number of different forms.

7. The applicant notes that, as the composition of the tomatoes is subject to natural fluctuations, the percentage of lycopene in the oleoresin can vary between 5 and 15%. The analysis of 25 commercial batches of the NI produced between 1995 and 2003 showed the range of lycopene levels (5.8%-15.6%) and total carotenoids levels (7.0%-16.5%) found in these products.

8. The levels of solvent residues, pesticides, microbiological contamination and heavy metals are assessed and any batches that do not meet the specifications for these criteria, as detailed in table 2 of the application dossier, are destroyed.

9. The applicant has evaluated the stability of the NI using nine batches of the NI. This showed no relevant changes in storage at 4°C and room temperature for up to 37 months. These data indicate that the product is stable at both temperatures.

Discussion: *The Committee was satisfied that the compositional analyses carried out on the NI show the chemical safety and the stability of the NI.*

II. Effect of the production process applied to the novel food
Application dossier p.16-23 Confidential

10. The production of the NI is identical to the production of the additive E160d, although E160d is subject to an additional concentration step to obtain an oleoresin that contains 60-70% lycopene.

11. The starting material for the production of the NI is tomato pulp. The tomatoes used to produce the NI are naturally selected, non-GM, hybrid, high lycopene content (150-220ppm) variety of tomato (Lycopersicon *lycopersicum*[13] L. Karst. ex Farw). The tomatoes have been specifically selected for their high lycopene content.

12. The production of tomato oleoresin is a two-step process:

    (i) The first step involves tomato pulp production. During this stage, the tomato is washed, crushed and screened. The juice is then heated using a heat exchanger at 80 to 90°C and centrifuged to produce the tomato pulp, which is analysed to confirm that the lycopene content is above 1,200ppm. The pulp is cooled, packed into laminate bags under vacuum and then placed into drums and stored at -18°C. The applicant has stated that this process introduces no exogenous substance and protects the tomato phytonutrients from oxidation, assuring that the subsequent extraction is conducted on unchanged and undeteriorated raw material.

    (i) The second step involves the extraction of lycopene from the tomato pulp. The pulp is crushed and extracted with ethyl acetate in a three-stage extraction process. The solvent is removed from the extract under vacuum at 40 to 60°C and the resulting oleoresin is analysed for lycopene content. Levels of solvent residues, pesticides, microbiological contamination and heavy metals are also analysed at this stage.

13. Batches that do not meet the NI specification on total lycopene level are reprocessed or blended with other batches to achieve the desired lycopene content. Lycopene levels can be increased by the partial removal of the tomato oil, which consists mainly of triglycerides without the dispersed lycopene crystals, by physical separation such as decanting or centrifugation. Lycopene is only slightly soluble in oil and therefore when the extraction solvent (ethyl acetate) is evaporated, lycopene precipitates forming a suspension of crystals in the tomato oil. No carrier oil or additives are added.

[13] *Lycopersicon lycopersicum* and *Lycopersicon esculentum* are synonyms for the tomato plant and come from different taxonomic schemes. They are used interchangeably in the literature.

14. The production of the NI is carried out in accordance with the principles of Food Good Manufacturing Practices using the Institute of Food Science and Technology Guidelines in Europe. The applicant has therefore stated that the production process is fully controlled to avoid the presence of relevant levels of toxicants and pathogens and allows traceability from the seeds through cultivation in the field to the finished product. Any products, which do not meet the standards, are rejected.

15. The final product consists of an oleoresin, which is packed in 1, 10 and 25kg bags under nitrogen in aluminium, high density polyethylene or plastic coated metal containers and stored at 4°C.

Discussion: *The Committee was satisfied that the production process of the oleoresin is the same as the production process of the approved food colour E160d, with omission of the final concentration step. Members also noted that appropriate controls were put in place on the production of the LRT tomatoes and throughout the production process of the oleoresin to ensure the safety of the final product.*

III. History of the organism used as a source of the novel food
Application dossier p.24

16. As mentioned in paragraph 4 above, high lycopene content tomatoes are used to produce the NI. This variety is not consumed per se, but is used for the manufacture of tomato paste in Israel and the USA (1000 tonnes of tomato paste is yearly produced in the USA from LycoRed LRT tomatoes). The applicant also states that "traditional and conventional breeding methods utilising the natural gene pool of the genus Lycopersicon have been applied in order to create a tomato plant with a high content of lycopene". This particular variety is not consumed directly but is used in production of tomato products.

Discussion: *The Committee was content with the information provided on the history of use of the lycopene-rich tomatoes used to produce the NI.*

IV. Anticipated intake/extent of use of the novel food
Application dossier p.25-26 and Appendix A p.3-12

17. The food categories to which the applicant wishes to add the NI are listed below. Given that the levels of lycopene in the NI vary (see paragraph 6), the actual quantity would be adjusted to achieve the desired lycopene concentration.

18. The applicant notes that the levels of incorporation are significantly lower than those permitted for use of lycopene as a food colour (E160d) (see table below).

Summary of LycoRed's proposed food uses and The recommend levels of use from tomato oleoresin in the EU				
Food category	**Proposed food use**	**Added lycopene (mg per portion)**	**Added lycopene (mg/kg)**	**Tomato oleoresin (g/kg)** (a)
Dairy Products	Yoghurts	5 (125g)	40	0.7
	Desserts/Custard	5 (125g)	40	0.7
	Cheese	5 (40g)	125 (b)	2.1
	Ice cream	5 (80ml)	62.5	1.0
Bread and baked goods	Bread	5 (30g)	167	2.8
	Biscuits	3 (20g)	150	2.5
	Fruit cakes/cake	5 (60g)	83	1.4
	Crispbreads	5 (50g)	100	1.7
Meat products	Sausages	5 (120g)	42 (c)	0.7
	Pates	3 (33g)	91 (c)	1.7
	Meat substitutes	5 (100g)	50	0.8
Juices	Fruit and Vegetable juices	5 (250g)	20	0.3
	Tomato juice	10 (120g)	83	1.4
Non-alcoholic flavoured drinks		5 (220ml)	23	0.4
Soups and sauces	Soup (other than tomato)	5 (220g)	23	0.4
	Tomato soup	10 (220g)	45	0.7
Cereal and cereal products	Breakfast cereals	5 (30g)	167	2.8
	Cereal bar	5 (25g)	200	3.3
Snack foods		2.2 (25g)	88	1.4
Pasta products (not canned)		5 (30g)	167 (c)	2.8
Fats spread	Margarine	3 (10g)	300 (c)	5.0
	Other spread	3 (10g)	300 (c)	5.0
Canned products	Baked beans	2.5 (150g)	17	0.3
	Canned pasta	5 (200g)	25	0.4

Notes:
(a) Assuming a lycopene content of 6%. (The product as proposed could contain 5-15% lycopene and the level of addition would be adjusted accordingly)
(b) Exceeds the limits set for use as a food colour
(c) Lycopene is not permitted to be added to this food category for colouring purposes

19. The applicant estimates that the total intake of the NI will vary between 6 to 45 mg of lycopene per day due to the variable use of supplements and fortified products in addition to the background intake from natural sources. Assuming a lycopene content of 6%, this is equivalent to 100-750 mg/day of the NI. Further information on dietary lycopene intake and bioavailablity is given in section 1 of Appendix A of the application.

Discussion: *Members are aware that the authorisation for the use of lycopene in the EU as a food additive was given on the basis of advice from the former Scientific Committee on Food in its 1975, 1983 and 1987 reports on the use of 'natural' food colours. The SCF did not have sufficient data to be able to set an ADI for the use of tomato lycopene as a colour and noted in 1987 that, as with other natural colours, "acceptance is limited to situations under which the use of colouring matters extracted from foods would not be expected to result in ingestion differing substantially from the amounts likely to be ingested from the normal consumption of foods in which they appear."*

Additionally, the Committee drew attention to the possible over-consumption of the oleoresin by children as a result of its presence in products such as ice cream, cakes and biscuits and highlighted the lack of data regarding the potential intake by infants (<1 year old) and young children (1-3 years old). The applicant has responded that it is not the intention of the company to target infants and young children in any of the food uses. The Committee therefore recommended that the labels of products containing the NI should indicate that they may not suitable for consumption by infants and children under the age of 3 years.

Concern was also raised by a member of the public on the consumption of the NI by male teenagers. The applicant has calculated that the margin of safety for individuals weighing 15kg or more was 90, based on results obtained from the 13-week oral toxicity study in rats which indicated a NOAEL of 4500 mg/kg bw/day. The Committee considered that the consumption of the NI by male teenagers did not raise any specific concerns.

V. Information from previous human exposure to the novel food or its source

Application dossier p.27-28 and Appendix A p.3-12

20. The applicant has used dietary composition studies from the Netherlands, Sweden, Finland, the USA and the UK to estimate the current consumption of lycopene naturally present in food such as tomato paste or sauces.

21. The applicant has indicated that intake from natural sources in the Netherlands shows an average lycopene intake of 1.05 – 1.56mg/day in men (max 26.1 mg/day) and 1.33 – 1.88mg/day in women (max 18.6mg/day) (Goldbohm et al, 1998). The Nordic Council of Ministers reported lower estimated lycopene intakes for Sweden and Finland of 0.34 and 0.26mg/day (Strube and Dragsted, 1999). An earlier study carried out by the Finnish Mobile Clinic Health Examination Survey gave a mean intake of 0.7 and 0.9 mg/day for men and women respectively (Jarvinen, 1995). Forman *et al* (1993) has estimated that daily intakes of lycopene in the US are in the order of 3.7mg. However, depending on the food products and supplements consumed in combination, intake can be as high as 15-30mg/day. A British study by Scott et al (1996) estimated that the mean daily consumption of lycopene-rich food gave about 1.1mg/day of lycopene.

22. The applicant notes that the dietary intake of lycopene as a food additive (E160d) is difficult to estimate because there are no dietary survey studies that look at the consumption of food additives in the normal diet. The use of existing dietary surveys is not possible because there are no available data on the amount of colour added to individual foods.

23. In addition to tomato and tomato products, the applicant has identified a number of other natural sources of lycopene that are minor components of the UK diet. Such foods are watermelon, red palm oil, guava and red grapefruit. Whilst these data indicate a range of different levels of intake, the use of lycopene in the EU, either as a food supplement or a food colour (E160d) is currently only permitted when it is obtained from a tomato source. It is therefore reasonable to assume that the background levels described by the applicant would have a similar compositional profile to the NI. The same data will also be indicative of the intake of other components present in the NI. A dose of 1mg of lycopene is equivalent to 7-20 mg of the oleoresin.

24. In order to estimate the background intake of tomato oleoresin arising from consumption of tomatoes and tomato products, the Secretariat has examined National Diet and Nutrition Survey data from 2001, covering British adults aged 16-64. The 97.5th percentile consumption of tomatoes – including the contribution of foods containing tomatoes and tomato products – was found to be 105 g/person/day. The lycopene content of the NI is 5-15%, and it is derived from LycoRed LRT tomatoes containing 150-250 mg/kg lycopene (see paragraph 5 above). The yield of the tomato oleoresin can therefore be estimated to fall within the range 0.1-0.5%, assuming complete recovery of lycopene. On this basis, high level tomato consumption of 105g/day is equivalent to 105-525 mg of tomato oleoresin.

Discussion: *Initially, the Committee queried why the application dossier had only provided information on previous human exposure to tomatoes and tomato products, but not the oleoresin. The applicant responded that over 400 tonnes of the NI were used in food supplements sold in Europe, the US and the Far East between 1995 and 2004. The applicant also noted that during this period, no adverse events related to the consumption of these food supplements were reported to LycoRed. The Committee was content with this additional information.*

VI. Nutritional information on the novel food
Application dossier p.29-32 of the application dossier and Appendix A p13-23

25. The applicant states that, whilst the lycopene component of the NI can be considered to be nutritionally equivalent to conventional tomatoes, tomato products and the additive E160d, small variations in the levels of other carotenoids and plant ingredients may occur due to the difference in the tomato varieties used and/or effects of the production process. The applicant is of the opinion that the addition of the NI to foodstuffs will not significantly affect their overall nutrient levels.

26. The potential health benefits of the introduction of lycopene into human diet are detailed in the application dossier. The findings of these studies do not have any bearing on the safety evaluation of the tomato preparation. They indicate that lycopene is an efficient oxygen quencher and has antioxidant properties which are reported to be associated with the inhibition of LDL oxidation/cholesterol synthesis. Finally, lycopene has been reported to enhance UV protection of the skin.

    Discussion: *The Committee was content with the nutritional information provided for the NI and did not consider the perceived benefits attributed to the consumption of lycopene.*

VII. Microbiological information on the novel food
Application dossier p.33

27. The production of the NI is controlled throughout and the final product is analysed in order to ensure its microbiological safety. The microbiological analyses carried out on the NI are listed in the application. The applicant has specified that the NI is produced without the aid of any microbiological processes.

    Discussion: *The Committee was satisfied that the applicant has demonstrated the microbiological safety of the NI.*

VIII. Toxicological information on the novel food

Application dossier p.34-42 and Appendix B

28. The applicant considers that the NI should not present any additional toxicological risks than those currently associated with tomato and tomato products. The applicant has not provided any information demonstrating the absence of tomatine, a toxic component found in unripe tomatoes, but concluded that the ripe tomatoes used to produce the NI would not contain tomatine. In response to a request for additional information from Members, the applicant highlighted that numerous scientific publications have shown that tomatine level declines during tomato ripening, whilst the lycopene content increases. The applicant will ensure that only red tomatoes are selected for the production of the NI. Finally, as tomatine is a polar molecule, it is unlikely to be extracted with the NI and would remain in the water phase. Two batches of the NI (containing 6% and 7% lycopene) were tested and tomatine was not detected at a limit of detection of 1ppm.

29. The applicant has provided a toxicokinetic evaluation of lycopene, using information obtained on [14C]-lycopene from secondary literature sources and not based on the evaluation of original papers or study reports. No differences in the toxicokinetic properties of lycopene between humans and rats have been observed. The applicant acknowledges that this information may not be representative of the toxicokinetic behaviour of lycopene in the NI.

30. A number of other toxicological studies, including acute toxicity (with irritation, skin sensitisation), semi-chronic toxicity and mutagenicity studies have been performed on the NI containing 5% or 6% lycopene. All these studies are detailed in Appendix B of the dossier and are outlined below.

31. **Acute toxicity, eye and skin irritation and skin sensitisation studies –** The acute oral and dermal toxicity of the NI at 5% on rats was found to be low with the LD50 levels greater than 5000mg/kg bw. The NI containing 6% lycopene was not found to be irritating to skin when tested on rabbits. However, results obtained in 1994 by Dreher, using 4 different batches of the NI containing 5% lycopene, showed that 2 batches out of 4 were irritating the skin of rabbits. Dreher used again these two batches for a sensitisation studies on guinea pig's skin and found one positive result. Although no analytical data were available on these two batches, the applicant explained that a problem with the lactic fermentation of the lycopene-rich tomato pulp, from which these two batches may have been derived, occurred in 1994 and could have induced these positive results. LycoRed has since changed their production process to prevent this fermentation problem, which was caused by the contamination with lactic acid bacteria, by introducing two analytical parameters in the control quality schedule. The applicant also states that the NI containing 5% or 6% lycopene did not irritate the eyes of rabbits.

32. **Semi-chronic toxicity** – A 13-week oral toxicity studying rats using daily doses by gavage of 0, 45, 450 or 4500 mg of the NI (containing 5% lycopene) per kg body weight (bw) was conducted. The staining of the tails detected on some rats was not considered to be relevant as this was attributed to accidental transfer of the NI during dosing. An increase in lung weight observed in female rats in the two upper dose groups was not accompanied by histopathological changes and was not considered to be an adverse effect. It was therefore concluded that the no-observed-adverse-effect-level (NOAEL) for this study was 4500 mg/kg bw/day[14]. This indicates a safety factor of 300, compared with the anticipated maximum intake of 45 mg added lycopene/day (see paragraph 19 above) for an adult of 60 kg (45mg of lycopene is equivalent to 900mg of the NI containing 5% lycopene, or 15 mg/kg bw)

33. **Mutagenicity studies** – The NI (5%) was negative in an Ames test, which used four batches of *Salmonella* and one batch of *E.coli*. Other mutagenicity studies of purified lycopene carried out by Collins (1998) and Riso (1999) did not show that lycopene had any mutagenic effects on human DNA. Although the applicant recognises that these studies are insufficient to assess the potential genotoxicity of the NI, which contains other components in addition to lycopene, they consider that there is no indication for genotoxicity.

34. Although it was not mentioned in the application dossier, a study conducted by Guttenplan et al (2001)[15] reported a pro-mutagenic effect of a lycopene-rich tomato extract when given to animals pre-treated with benzo[a]pyrene, a known carcinogen. The applicant suggested that this study has to be viewed in the context of a number of other studies showing that lycopene preparations protect animals against tumour induction. The applicant also expresses doubt about the identity of the test substance used in this study. In particular, the material has a very much higher beta-carotene content than could be expected from lycopene-rich tomato oleoresin. The applicant noted that the test substance has the trade name 'Betatene', which has been used for some years for carotenoid mixtures derived from micro-algal sources. The applicant suggests that the material used for this study may have been a blend of tomato lycopene and algal carotenoid-rich extract.

35. No data on reproductive/developmental toxicity and teratogenicity of the NI were submitted in this application.

Discussion: *The Committee was specifically concerns about the following aspects of the toxicological assessment of the NI:*

[14] This figure is misquoted as 24500 in Appendix B (p.28) of the application dossier.

[15] Guttenplan J. B., Chen M., Kosinska W., Thompson S., Zhao Z., Cohen L. A. (2001) Effects of a lycopene-rich diet on spontaneous and benzo[a]pyrene-induced mutagenesis in prostate, colon and lungs of the LacZ mouse. Cancer letters 164 (2001), 1 – 6

(i) ***Skin sensitisation study*** *– Members were concerned that results obtained on two out of 4 batches of Lyc-O-Mato® 5% were positive in the skin irritation test. The applicant suggested that this issue had been resolved by changes to the production process to prevent the lactic fermentation of the lycopene-rich tomato pulps. However, Members recommended that this hypothesis should be tested by repeating the study with more recent batches of the product. The applicant consulted an expert for advice, who confirmed that the positive results obtained on the 2 batches produced in 1994 was due to the fermentation problem causing high acidity (pH 3.1-3.5) from the high citric acid level (2.5-3.6%). This manufacturing process was revised in 1995 which resulted in oleoresin batches with higher pH (4.5-4.7) and lower citric acid level (0.3-0.5%). Batches from 1995 were tested on rabbits and guinea pigs and it was found that neither skin irritation nor contact hypersensitivity were induced by the NI. The Committee accepted this additional confirmation and concluded that the NI did not cause skin sensitisation.*

(ii) ***Semi-chronic toxicity study*** *– in their initial consideration, the Committee requested that detailed histopathological data be provided by the applicant to clarify the significance of the increase in lung weights that was observed for female rats in the upper dose groups. The applicant provided some additional information and the Committee requested that a toxicologist with expertise in animal pathology be contacted in order to assess the significance of the findings. The nominated expert confirmed that the observed increased absolute lung weights was not indicative of a target organ toxic effect and related to the body weight increases for rat females, caused by treatment. The Committee agreed with the advice and concluded that the 4,500 mg/kg bw/day exposure level could be taken as the NOAEL in this study.*

(iii) ***Mutagenicity studies*** *– the Committee was satisfied that the NI is not genotoxic. The Committee asked that initial statements made by the applicant regarding the absence of tomatine should be backed up by additional data and was satisfied with the additional information provided by the applicant on this point.*

Allergenicity and labelling
Application dossier p39-40

36. In their dossier, the applicant accepts that whilst there is little information available on tomato allergens, some individuals are known to be allergic to tomatoes. A study by Westphal et al (2004) concluded that tomato profilin is a minor allergen and can induce immunological reaction in tomato-allergic individuals.

37. The applicant originally indicated that due to the nature of the oleoresin, they were unable to accurately quantify the level of proteins in the NI. The applicant therefore suggested that, as the NI originates from tomatoes, the NI would be described as a "tomato extract containing lycopene", which will alert any consumers who seek to avoid eating tomato products. Members requested that the applicant investigated alternative methods of protein analysis. The applicant provided results obtained using a SDS-PAGE method followed by silver staining.

Discussion: *There were technical problems associated with the measurement of proteins in the NI and with the SDS-PAGE analysis. Whilst the latter gave some reassurance, the Committee was of the view that the protein analysis did not categorically demonstrate that the NI was free from allergens. In view of the low level of tomato allergy in the population, Members were content that the provision of clear labelling offered adequate protection for consumers who are sensitive to tomato allergens.*

Overall discussion

38. The applicant has provided details on the specification of the proposed novel food ingredient, which has a lycopene content of between 5 and 15%. This variation is due to the composition of its tomato source, which is subject to natural variation. The production process is essentially the same as that for the approved food colour E160d.

39. The information supplied by the applicant offers sufficient reassurance that consumption of the NI does not give rise to any toxicological or allergenic concerns.

40. The applicant has demonstrated that the NI is stable at ambient and refrigerated temperatures. The applicant has also demonstrated that this NI is microbiologically safe by applying a quality control system throughout its production process.

41. Regarding the labelling of the product, the applicant needs to comply with the Food Labelling Regulations 1996 (as amended). They should also ensure that the labelling and presentation of the products does adequately inform the consumer, particularly in relation to its consumption by infants and children under the age of 3 years.

Conclusion

42. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by LycoRed that the range of uses for its lycopene-rich oleoresin 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 the NI should be labelled in accordance with existing legislation and should not make claims that are likely to mislead consumers. The labelling should also indicate that these products may not be suitable for infants or young children under the age of 3 years.

30th June 2002

APPENDIX V

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on an application under the novel foods Regulation for d-tagatose

Applicant	Bioresco, on behalf of Arla Foods, Denmark
Responsible Person	Dr Albert Bär
EC Classification	2.1

Introduction

1. An application has been submitted by Bioresco, acting on behalf of Arla Food Ingredients, Denmark for authorisation of D-tagatose as a novel ingredient in the EU.

2. D-tagatose is a monosaccharide, an enantiomer of D-fructose (inversion at C-4), which is not commonly found in food, although it is found at low levels in heat-treated dairy products such as sterilised and dried milk. D-tagatose has 75-92% the sweetness of sucrose and behaves like other sugars in terms of hygroscopicity, and stability under low pH and raised temperature. Its principal purpose is as a carbohydrate source, with purported nutritional effects of non-cariogenicity and as a prebiotic. During preliminary discussions with the applicant, the Secretariat noted that the use of D-tagatose in foods could fall within the legal definition of a sweetener, requiring authorisation under food additive legislation rather than the regulation on novel foods. This issue has been resolved following discussion with the Commission and other MS and the consensus view is that tagatose should be regarded as a novel food ingredient and not as a food additive.

3. This opinion details the safety of this novel ingredient and does not investigate or comment on the perceived nutritional effects that the applicant attributes to its consumption.

I. Specification of the novel food

Information on this aspect is provided on pp 14-16 and pp25-27, Annexes 1, 3 and 4 of the application dossier

4. As an enantiomer of D-fructose, D-tagatose has the empirical formula $C_6H_{12}O_6$ (see Figure 1). An overview of the compositional analyses of D-tagatose and the raw materials used in its production

are given in Annex 1, sections 3 and 5. Detailed information on the specifications of raw materials, process chemicals and ion exchange resins are listed in Annex 1.

5. The novel ingredient (NI) is synthesised by enzymatic hydrolysis from lactose with a purity of ⩾99%. All chemicals used in the production process are high purity and have low levels of heavy metals (Annex 1). The resulting D-tagatose has a purity of no less than 98%, a lead content no greater than 1 ppm and an ash content of no more than 0.1%.

6. D-tagatose is produced from lactose using a two-step process. In the first instance lactose is enzymically hydrolysed to galactose and glucose. The galactose is then isomerised to D-tagatose at a high pH using calcium hydroxide as a complexing agent.

7. Batch-on-batch variation has been determined by analysis of 6 batches of D-tagatose, produced by the applicant at pilot scale (Annex 4). These indicate a high degree of reproducibility. HPLC data (Annex 4) show that the only detectable impurity in the final product is galactose, which is present as a by-product of the production process.

8. D-tagatose has been evaluated by JECFA[16] on three occasions, most recently in 2004 when it allocated an ADI "not specified"[17]. The detail of the toxicological evaluation by JECFA is discussed later in this paper. The JECFA specification for D-tagatose is given in Annex 3.

Discussion *Members were satisfied with the specification of the novel food.*

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

Information on this aspect is provided on pp 17 – 24 of the application dossier

9. D-tagatose is produced from food-grade lactose by a two-stage process involving enzymatic hydrolysis of food-grade lactose to form galactose, which then isomerises to D-tagatose under alkaline conditions. The applicant has summarised the process on p17 and included a detailed flow diagram (Figure 2).

10. All chemicals used in the production process including the raw material (lactose) and the immobilised lactase (obtained from Aspergillus oryzae) are food grade, as are all anti-microbials and column regeneration chemicals.

[16] **JECFA:** Joint FAO/WHO Expert Group on Food Additives.

[17] **ADI Not Specified:** Used by JECFA to refer to a food substance of low toxicity which on the basis of the available data, the total dietary exposure necessary to achieve the desired effect, and acceptable background levels in food does not represent a hazard to health.

11. Process
Lactose is first dissolved in hot water and the pH is adjusted, by addition of lactose solution that has been passed through an ion exchange column, to obtain a mildly acidic solution. This solution is then pasteurised before being passed through a column that contains immobilised lactase. This enzyme preparation is widely used throughout the EU. To avoid contamination, the column is regularly treated with a defined anti-microbial solution.

12. The resultant hydrolysed lactose solution is concentrated by evaporation before being fractionated using a cation exchange resin. The resultant fractions are collected and the galactose-rich fraction retained. This fraction is cooled and the galactose is converted to D-tagatose by addition of a defined amount of $Ca(OH)_2$, which moves the isomerisation equilibrium in favour of the D-tagatose. D-tagatose is precipitated as an insoluble complex with calcium. Once this stage is completed the NI is removed and re-dissolved by addition of CO_2 which neutralises the mixture and causes precipitation of the calcium as $CaCO_3$.

13. Purification
The NI is purified by filtration, evaporation, demineralisation, and fractionation. These are described in detail on pages 20-22 of the application dossier.

14. The applicant notes that the conditions used to produce the NI are relatively benign and do not favour other reactions that could potentially occur, particularly during the isomerisation of D-galactose. A brief discussion of the potential impurities that could arise as a result of the occurrence of these 'side reactions' is detailed on page 25. None of the compounds described were found in detectable quantities in the end product (Annex 4).

Discussion *Members were content that the production process employed by the applicant does not give rise to concern*

III. Anticipated intake/extent of use of the novel food
Information on this aspect is provided on pp 33-46 and Annex 6 of the application dossier

15. The applicant intends the NI to be used as a nutritive ingredient in a variety of products. The availability of these products will not be restricted geographically and there are no plans to target these products at particular consumer groups. A list of products and the levels at which D-tagatose is typically expected to be added can be found in the table below:

Food Category	Proposed food use	Added Tagatose (g per 100g of food)
Baked goods	Cookies	2
	Quick breads	2
	Muffins	2
	Quick bread type	2
	Coffee cakes	2
Beverages	Diet" and "sugar- free" carbonated beverages; non-carbonated Beverages sweetened with low- calorie sweeteners – includes milk-based beverages, juices, juice drinks, teas, and coffee- based Beverages (ready- to- drink, prepared from mix, and dry mix forms)	1
Coffee drinks	Such as cappuccino and latte	1
Frozen milk based desserts, reduced/low fat	Light ice cream	3
	Frozen milk desserts	3
	Low fat and non fat frozen yoghurts	3
	Related frozen novelties	3
Hard candies	Hard candies including regular and dietetic candies	15
Health bars and diet soft candies	Low fat, reduced fat, diet meal, energy or nutrient fortified bars, dietetic soft candies	10
Icings	Icings (or glazes), such as those used on cookies, pastries, brownies, and angel food, chiffon, and pound cakes	30
Meal Replacement/ supplement Beverages	Meal replacement beverages, diet meal beverages, nutrient supplement beverages (ready- to- drink, prepared from mix, and dry mix forms)	5g per 240 ml serving (2.08g per 100g)
	Protein drinks, including supplements and diet beverages (ready- to-drink, prepared from mix, and dry mix forms)	1
Milk chocolate	Milk chocolate candies and coatings/coverings	3
Ready-to-eat cereals	All ready-to-eat cereals	3g per 5-55g serving (5-20g per 100g)
Smoothies	Fruit and dairy "smoothie" type beverages	1
Soft/chewy candies	Soft/ chewy candies such as caramels, toffees, taffies, nougats,Creams, fudges, fondant, and fruit- based confectionery (excluding Marshmallows, soft jellies, gummies, panned candies, and liquorice)	3
Chewing gum	Tooth friendly (non-cariogenic) chewing gum	30
Table top sweeteners, low calorie	Sugar substitutes/replacements	1g per serving
Yoghurt	Yoghurt	2

16. The applicant has used dietary survey data to estimate the likely consumption of tagatose in the United States population. These data were taken from the 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII) on US households and from the 1998 CSFII on children aged 0-9. The data were collected using 24-hour recall interviews for two non-consecutive days and defined according to time and eating occasions. In all cases, it was assumed that all foods or ingredients in each category would contain the NI

at the level stated in the table above. A more detailed breakdown and discussion is given in Annex 6 of the dossier. The table below provides a summary of the estimated intake of the NI for US population older than 2 years old:

Summary of the estimated intake of D-tagatose from its proposed food use (excluding chewing gum and food supplements)					
Population	Age	2-day average intake of D-tagatose			
		g/person/day		g/kg bw/day	
		Mean	90th Percentile	Mean	90th Percentile
Children	2-5	3.2	6.2	0.19	0.37
Young schoolchildren	6-12	4.3	8.5	0.14	0.28
Teenagers	13-19	4.7	9.5	0.08	0.16
Adults	> 20	4.8	10.5	0.06	0.14
Total population	> 2	4.6	9.8	0.08	0.19

17. The intake of the NI from sugarless chewing gum was based on the results from a separate US survey carried out in 1995. The results of this survey indicate that the average gum consumption in the US population was 2.5 pieces per day. The equivalent figures for pre-school children and teenagers were 1.6 and 3.0 per day. (Annex 6 Table 26).

18. The applicant states that, for technological reasons related to the production of tablets, the intake of the NI via the consumption of food supplements is unlikely to exceed 3g/person/day. The applicant has not explained the derivation of this figure.

19. In response to a request from the Committee, the Secretariat compared the data obtained from the US dietary survey data with the UK NDNS data. The results, calculated using the closest matching food categories are detailed below. These data show comparable levels of consumption would be seen in the UK population.

Comparison of intake estimates based on US and UK dietary survey data					
US Data (g/person/d)			UK data (g/person/d)		
Age Group	Mean	90th %ile	Age Group	Mean	90(97.5) th %ile
Pre-school (2-5 years)	3.2	6.2	Pre-School (1½– 4½ years)	2.8	6.9 (10.3)
School Children (6-12 years)	4.3	8.5	School Children (4-18 years)	5.6	11.9 (17.7)
Teenagers	(13-19 years	4.7	9.5		
Adults (> 20)	4.8	10.5	Adults (18- 64)	3.7	9.7 (11.6)

Discussion *Estimates of D-tagatose intake for the US and British populations are similar, based on the list of expected uses provided by the applicant. Members noted that higher levels of intake could result in future if the range of uses was expanded or if D-tagatose is incorporated at higher levels.*

IV. Nutritional information on the novel food

Information on this aspect is provided on pp 28-34 of the application dossier

20. Reduced Energy Value. Studies described by the applicant indicate that D-tagatose is incompletely absorbed and therefore has a lower energy value compared with sucrose. The applicant refers a number of studies that indicate that the NI has an energy value of 1.5kcal/g. This figure is significantly lower than the value of 4kcal/g that currently applies for the labelling all sugars as specified in the Nutritional Labelling Directive (90/496/EC).

21. Lower glycaemic impact and prebiotic activity. A number of studies were described by the applicant in the dossier. These do not have any bearing on the safety assessment of the novel ingredient.

Discussion *Members agreed that the studies provided by the applicant in relation to the efficacy of the novel ingredient were not relevant to the safety assessment. It was noted that current European Community nutrition labelling rules require that sugars are labelled to indicate that they supply 4 kcalories/g. A more appropriate value can only be applied for D-tagatose if the applicant seeks an amendment to the Nutrition Labelling Directive (90/496/EEC).*

V. Microbiological information on the novel food

Information on this aspect is provided in Annex 4 of the application dossier

22. The production of the NI does not involve the use of micro-organisms. The microbiological purity of D-tagatose is detailed in tables 1 and 2 of Annex 4. These data indicate that the final product is essentially free from microbial contamination.

Discussion *Members agreed that the production does not involve the use of a micro-organism and were content that the production process employed by the applicant does not give rise to concern.*

VI. Toxicological information on the novel food

Information on this aspect is provided on pp p 44-111 of the application dossier

23. Biochemical Aspects (Absorption, distribution and excretion)
The applicant presents a number of studies that indicate a variable and incomplete absorption of D-tagatose. One study also details a pronounced increase in the short chain fatty acids in the blood. SCFA's are produced by bacterial fermentation of the unabsorbed NI in the large intestine. The applicant refers to this 'prebiotic' effect as a tangible benefit that can be attributed to the consumption of the NI.

24. Several studies carried out on humans indicate that intestinal side effects, including stool softening, may occur in susceptible individuals after the consumption of more than 15g D-tagatose (ingested in a single sitting). The tolerable daily dose is a multiple of the tolerable single dose as the intestinal effects are not cumulative over time.

25. Metabolism
The applicant has referred to a number of scientific studies that demonstrate that the metabolism of D-tagatose takes place along well defined biochemical pathways. Following an initial phosphorylation step, the metabolism converges with the pathway seen for fructose.

26. Toxicological studies
The applicant includes reports from a number of animal studies, which are listed below. The applicant has also conducted four studies indicating a lack of genotoxicity. These studies have also been reviewed by JECFA, which considered D-tagatose three times during 2001-2004. The initial JECFA evaluation of D-tagatose highlighted a number of questions concerning, glycogen deposition and hypertrophy in the liver, and increased serum levels of uric acid.

27. The applicant commissioned a number of additional studies that paid particular attention to these parameters, and following a detailed evaluation JECFA allocated an ADI "not specified" for D-tagatose at its 63rd Meeting in June 2004. The applicant has submitted the same data for novel food approval.

Genotoxicity studies				
Test	**Test system**	**Concentration**	**Results**	**Reference**
Bacterial gene mutation [a]	*S.typhimurium* (TA 1535, TA 1537, TA1538, TA98, TA100); E.coli (WP2uvrA)	100-5000 mg/plate	Negative	Lawlor, 1993; Kruger, 1999a
Chromosomal aberration [a, b]	Chinese hamster ovary cells	1250-5000 mg/ml	Negative	Murli, 1994a; Kruger et al., 1999a
Micronucleus formation [d]	CD-1 mouse bone marrow	1250-5000 mg/bw (p.o.)	Negative	Murli, 1994a; Kruger et al., 1999a
TK-locus mutation [a, c]			Negative	

a) With and without exogenic metabolic activation (rat liver S9 fraction).
b) Treatment time, 7.4h (without activation), 2h (with activation); harvest time 10h
c) Treatment time, 4h
d) Termination 24, 28 and 72h after dosing

Animal studies					
Type of study	**Species (N)**	**Dose level (% of diet or g/kg bw)**	**Results**	**NOAEL (% of diet and/or g/kg bw/d)**	**References**
acute toxicity test	Rats (5M, 5F) Mice (5M)	10g/kg bw (single dose)	no mortality or reaction to treatment	10g/kg bw	Trimmer, 1989
Subchronic (90-d) toxicity study	S-D rats (20M 20F / group)	0,5,10,20% 10% fru + 10% cellulose	soft stool (day 1-3); reduced weight gain in 20% group; increased abs. and rel. liver weights in 10, 15, 20% tag groups, some hypertrophy of hepatocytes in 15, 20% group [a]	5% [c]) [3.7 (F) and 4.1 (F) g/kg bw/d]	Trimmer et al., 1993 Kruger et al., 1999c
Subchronic (29-31 d) study on liver parameters [d]	S-D rats (20M / group)	0,5,10,20% tag	Dose dependent increase of liver glycogen and lower weight [b]). No ultrastructural (EM) changes of liver tissue except increased glycogen deposition. Slight increased ALAT, ASAT in 20% tag group probably in response	n.d [d])	Lina et al., 1998 Bar et al., 1999
Subchronic (6-month) toxicity study	Wistar rats (60 F/group)	0, 5, 10% tag, 20% fru, 10% tag + 10% fru Interim kills on day 3, 7, 14, 28, 94, 128 (10F / group)	Only liver and plasma parameters were examined. No increase of liver weight and no histopathological changes [a]) ; no changes of plasma parameters.	10% of diet [5.8 g/kg bw/d (day 1-28); 4.8 g/kg bw/d (day 1-28)]	Lina & de Bie, 2000d
Chronic (24-month) toxicity/carcinogenicity study	Wistar rats	0, 2.5, 5, 10% tag, 20% fru, 10% tag + 10% fru	Examination of organ weights and his topathology limited to liver, kidneys, adrenals and tests (cecum: weight only). Liver enlargement in 10% tag (M), 20% Fru (M), 10% tag +fru (M&F) but no morphological changes. Increased nephrocalcinosis in females of all tag dose groups and in 10% tag	2.5% of diet [< 1 g/kg bw/d]	Lina & Kuper, 2002 Lina & Bar, 2003

Animal studies					
Type of study	Species (N)	Dose level (% of diet or g/kg bw)	Results	NOAEL (% of diet and/or g/kg bw/d)	References
			(M) and 10% + 10% fru (M). increased incidence of adrenomedullary proliferative disease in 2.5% tag (M), 5% tag (M & F), 10% (M & F) and 10% + 10% fru (M&F)		
Energy balance study (33-d)	Pigs (2 / group)	0, 20% tag, 20% suc, 10% tag + 10 % suc	No ultrastructural (EM) changes of liver tissues	5 g/kg bw/d	Mann, 1997
Embryotoxicity / teratogenicity study (range finding)	S-D rats (5M / group)	0, 4, 8, 12, 16, 20 g tag/kg bw/d (day 6-15 of gestation)	Soft stool and diarrhoea at 12 g/kg bw. (No adverse effect otherwise).	20 g/kg bw/d (11 g/kg bw/d)	Schroeder, 1994a
Embryotoxicity / teratogenicity study	S-D rats (24M / group)	0, 4, 12, 20 g tag/kg bw/d (day 6-15 of gestation)	Maternal liver weight increased in 12 and 20 g/kg bw group. No morphological changes in liver. No adverse effects otherwise.	20 g/kg bw/d	Schroeder, 1994b; Kruger et al., 1999b

Key: M = Male, F = Female

Abbreviations: tag, D- tagatose; fru, fructose; suc, sucrose; ALAT, alanine aminotransferase; ASAT, aspartate minotransferase; S-D, Sprague-Dawley; n.d., not determined; bw, body weight.

a) Animals killed after overnight fasting

b) Animals killed in the fed condition

c) Based on effects on liver weight

d) Liver weight cannot be used as a basis for determination of the NOAEL since rats were killed in the fed condition (increased weight is partly due to liver glycogen accumulation). D- Tagatose intake was about 11.4 g/kg bw/d at the high-dose level.

e) A series of additional studies on the effects of D- tagatose on liver weight and glycogen accumulation was performed but their results are not shown in this table because toxicological end- points (e.g.,histopathology)were not examined.

Discussion *The novel ingredient has been subject to a number of toxicological studies. The Committee noted the toxicological assessment by JECFA in 2004 and agreed with the expert group that the data did not highlight any toxicologically significant findings, and exhibited properties that were similar to other carbohydrates of other low digestibility.*

Allergenicity and Labelling

Information on this aspect is provided in p 109-110 and Annex 4 of the application dossier

28. The NI is manufactured from crystalline lactose, obtained from cheese whey, which contains protein at levels of up to 0.2%. Recognising the known allergenic potential of milk and derived products, the applicant has demonstrated the absence of whey protein in the NI using an ELISA method. (<10□g protein equivalent / g NI, see Annex 4). The same assay detected protein in 2 (of 3) lactose samples tested.

29. The applicant speculates that the absence of whey protein is to be expected due to the production process, which involves the use of heat-treatment, high pH, ion-exchange resins and activated carbons.

30. In their consideration of the product JECFA concluded that ingestion of 30g or more of the NI may cause gastrointestinal effects in humans. The applicant has also suggested that no warning on laxative effects is necessary for foods listed in the table containing D-tagatose because the maximum intake of D-tagatose would be extremely unlikely to exceed 10g per eating occasion for consumers of any age group (see Table 3 of application dossier). This statement is based on high level US consumption data using figures at the 90th percentile. Estimates using UK NDNS data are similar. The applicant has also acknowledged that the products described in the table are indicative of intended use only, and it would be appropriate to label any foods containing more than 15g of D-tagatose per serving with the statement "excessive consumption may produce laxative effects". This text is in line with the current requirement for polyols (Directive 96/21/EC) which applies to foods containing more than 10% polyols. The applicant's proposal will cover all food categories and is based on the intolerance being induced by the amount, rather than concentration. Unlike polyols, tagatose is proposed for certain beverages, where higher levels of intake may be achieved at a lower concentration of D-tagatose.

31. Following a specific request by the Committee, the applicant submitted additional data to demonstrate that the proposed labelling described above was equally applicable to children as well as adults.

Discussion *Members noted that although the applicant provides evidence that the NI is unlikely to contain whey proteins, the product is derived from a milk source. A new amendment (2003/89/EC) to the food labelling directive (2000/13/EC) requires specified food allergens and their derived ingredients to be included in ingredients listing. Milk is a specified allergen and this requirement therefore applies to the novel ingredient, irrespective of the manufacturing process, unless the applicant applies to the Commission for a formal exemption. Members wished to note that it was their view that the data provided to demonstrate that the product was free from milk proteins was unlikely to offer sufficient grounds to qualify for an exemption.*

Concerning the potential for exerting a laxative effect, the Committee noted the proposal for labelling on the basis of consumption of more than 15g of the NI in a single serving, similar to the labelling requirement for polyols set out in Directive 96/21/EC. There are no data on the effects of tagatose consumption amongst children although young children are known to be generally more prone to diarrhoea, probably because they have a less developed GI tract. The limited data available on other poorly absorbed compounds, such as sorbitol, indicate that pre-school children may be more sensitive than adults and older children. The applicant does not intend the ingredient to be used in foods specially manufactured for young children but it is likely that they will consume general foods that contain D-tagatose, particularly soft drinks. The Committee therefore considered that the labelling criterion proposed by the applicant is appropriate for solid foods, but proposed that all beverages containing more than 1% D-tagatose should also carry the same advisory labelling.

General discussion

32. Members noted that D-tagatose has been subjected to thorough toxicological testing and agreed with the conclusion of JECFA that it is a substance of low toxicity and does not represent a hazard to health.

33. Like other poorly absorbed compounds, D-tagatose may cause mild gastrointestinal effects in high level consumers. The individual doses of D-tagatose associated with these effects is in the range 15-30 grams which is unlikely to be achieved from consumption of the tagatose-containing foods described by the applicant. Nevertheless, the range of uses may be extended in future and Members supported the applicant's proposal to include advisory labelling on any food product that contained in excess of 15g D-tagatose per serving as being adequate to ensure that consumers were advised of the effect of potential gastrointestinal intolerance. To take account of consumption by young children, and because of evidence that poorly-absorbed compounds may exert a greater laxative effect when taken in liquid form, this advisory labelling should also be applied to all beverages containing more than 1% D-tagatose.

34. Members also noted that allergen labelling as defined in amendment 2003/89/EC to the food labelling directive (2000/13/EC) will apply to all products that contain the NI, unless the applicant applies to the Commission for a specific exemption to be incorporated into the relevant directive.

Conclusion

35. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by Bioresco on behalf of Arla Foods that D-tagatose is acceptable, subject to the applicant's adherence to the proposed specification and the labelling requirements described above.

9 August 2005

APPENDIX VI

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

Opinion on sustantial Equivalence of Noni Juice considered under Article 5 of the Novel Foods Regulation

Applicant	Mi GmbH
	Rigistrasse 116
	CH-6340 Baar
	Switzerland
On behalf of	Mi GmbH Switzerland and Mi EU Ltd. UK
Responsible Person	Garry Martin

Introduction

1. A request was submitted by Mi GmbH and Mi EU Ltd. to the UK Competent Authority for an opinion on the equivalence of their noni juice ingredient to the noni juice ingredient produced by Natures Products and marketed by GSE Vertrieb in the EU by substantial equivalence in the UK.

2. Noni juice is produced from the fruit of the plant Morinda citrifolia L. that is commonly grown in the Pacific region where the juice is traditionally consumed.

3. According to Article 3(4) of Regulation (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 as regards their:

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

Composition

4. The applicant is claiming equivalence to the Noni Juice produced by Natures Products and marketed for sale in the EU by GSE Vertrieb.

5. The applicant initially provided compositional analysis of two samples of their noni juice and one sample of the Natures Products noni juice. The Committee requested additional samples to be tested in order to demonstrate that their noni product did not differ from the approved counterparts. The applicant provided three additional sets of compositional data for Mi GmbH noni and three for Natures Products.

	Mi GmbH Mean ± SD (5 Samples)	Natures Products Mean ± SD (4 Samples)
Parameters		
Minerals g per 100ml	0.46 ± 0.04	0.58 ± 0.07
Total Protein NX6.25 per 100ml	0.24 ± 0.04	0.38 ± 0.16
Alcohol vol %	0.26 ± 0.09	0.31 ± 0.08
Potassium mg per 100ml	187.4 ± 20.08	246 ± 28.9
Magnesium mg per 100ml	11.48 ± 1.08	15.4 ± 2.17
Sodium mg per 100ml	11.02 ± 3.13	12.2 ± 2.87
L-(+)-Lactic Acid g per Litre	0.64 ± 0.72	1.71 ± 0.39 (3 Samples)
D-(-)- Lactic Acid g per Litre	0.55 ± 0.87	1.51 ± 0.48 (3 Samples)

6. The product produced by the applicant is manufactured in the same way as the approved noni product. However the fruit is pulped and frozen before being shipped to Switzerland, a process that is routinely used to transport noni prior to processing. It is then shipped to Switzerland where it is bottled using the same processes as Natures Products, except that it is ultrafiltrated before it is pasteurised.

Discussion: *The Committee was content that the expert opinion and the compositional analysis demonstrated that the applicant's product is substantially equivalent to the existing product. Members were content that the variations seen between the different noni juice samples were consistent with natural variation.*

Intended use

7. The applicant intends to market their noni juice in 5 different forms:

- A pasteurised Juice (Direct Squeeze/Fresh Squeeze)
- Direct/fresh juice with up to 2% added concentrate (pure noni)
- A concentrate
- A frozen concentrate
- A frozen pasteurised juice

8. The recommended consumption in each case is 30ml/day, which is the same as for the noni juice that has already been authorised. The concentrated juice is to be supplied only to industry and the final product will be sold to the consumer in a diluted form with a recommended intake of 30ml a day.

Discussion: *The Committee was content that the applicant's noni juices it to be consumed at the level and in the same form as the existing product.*

Nutritional Value and Metabolism

9. The applicant has demonstrated that the noni juice is substantially equivalent to Natures Products noni juice even though the pulp is frozen and the juice is ultrafiltrated before it is bottled. There is no evidence in the application to suggest that the nutritional value and metabolism will differ significantly from the product currently permitted on the market in the EU.

Discussion: *The Committee was content with the evidence provided by the applicant demonstrating that nutrient content was equivalent to the existing product.*

Level of Undesirable Substances

10. The applicant has demonstrated that there are no detectable levels of Escherichia coli or Salmonella or aerobic bacteria in the pasteurised juice. In order to minimise the risk of anthraquinones the applicant has informed us that all leaves and twigs are removed by hand post harvest. The applicant has also demonstrated that no pesticide residues were detected in the juice at or above the limits of detection.

Discussion: *The Committee was content that the applicant had provided sufficient evidence that their product was substantially equivalent to the existing noni juice product in terms of undesirable substances. Members noted that the applicants will implement measures to ensure that subsequent batches of the juice produced are similarly free from undesirable substances.*

Conclusion

11. The Committee is content that the applicant's approach to demonstrating the equivalence of Mi GmbH's noni juice with the existing noni juice ingredient is consistent with the criteria set out Article 3(4) of the Novel Foods Regulation (EC) 258/97. The applicant's product is manufactured and marketed in a way that is substantially equivalent to Natures Products noni juice. Data on the composition of noni juice suggest that freezing and ultrafiltration production steps do not have any major effects on the composition of the juice.

12. Therefore noni juice produced by Mi GmbH and Mi EU Ltd can be considered to be substantially equivalent to the existing noni juice produced by Natures Products.

APPENDIX VII

ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES

Opinion on sustantial Equivalence of Phytosterols considered under Articla 5 of the Novel Foods Regulation

Applicant Prima Pharm BV

15, Nieuwe Uitleg

2514BP Hague

Netherlands

Responsible Person Mr M. Jaume Torres

Introduction

1. A request was submitted by Prima Pharm to the UK competent authority for an opinion on the equivalence of their phytosterols to the phytosterols marketed by Teriaka which were authorised by Commission Decision 2004/336/EC. In July 2004 and October 2004 Teriaka obtained opinions on equivalence from the Finnish competent authority that extended the range of foods that their phytosterol ingredient could be incorporated into. These are, yellow fat spreads, milk based fruit drinks, yoghurt type products, cheese type products, milk type products, soya drinks, and fermented milk products. Teriaka notified the Commission of the placing on the market of their products in accordance with Article 5 of regulation (EC) 258/97 on 16 July 2004 and 16 November 2004. Prima Pharm are therefore entitled to seek a view on equivalence for the use of their phytosterol ingredient in each of the food categories included in Teriaka's original authorisation and the two subsequent notifications granted by the Finnish competent authority.

2. 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 as regards their:

- Composition
- Nutritional Value

- Metabolism
- Intended use
- Level of undesirable substances contained therein."

Composition

3. The Applicant is claiming equivalence to the specification of phytosterols set out in Annex 2 of Commission Decision 2004/336/EC. Prima Pharm obtain their phytosterols from the company les Derives Resiniques et Terpeniques (DRT). It should be noted that the data on DRT's tall oil phytosterols were included in Teriaka's original novel food application, along with data from another supplier of phytosterols derived from vegetable oils. However, although DRT's phytosterols have been through the authorisation process they have not been used by Teriaka since gaining approval.

4. The product produced by the applicant is made from tall oil pitch from Pinus maritima (synonym Pinus pinaster) a species of pine tree. It is manufactured in the same way as the approved phytosterol product and involves extraction, crystallisation and drying. The specification of the product described by the applicant is consistent with that described in Commission Decision 2004/336/EC.

5. To comply with the conditions set out in Commission Decision 2004/336/EC for phytosterols and phytostanols extracted from sources other than vegetable oil, all batches of the product will have a purity of more than than 99%.

Discussion: *The Committee noted that data provided on the composition of Prima Pharm's phytosterols complied with the specification of phytosterols in Commission Decision 2004/336/EC.*

Nutritional value and metabolism

6. The nutritional value and metabolism of Prima Pharm phytosterols are expected to be the same as those marketed by Teriaka. 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.

Intended Use

7. The applicant intends the ingredient to be used in yellow fat spreads, milk based fruit drinks, yoghurt type products, cheese type products, milk type products, soya drinks, and fermented milk products. These products are the same as existing products on the market containing Teriaka phytosterols that were authorised in Commission Decision 2004/336/EC and the two subsequent notifications issued by the Finnish competent authority in July and October 2004.

Discussion: *The Committee is 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.*

Level of Undesirable substances

8. The applicant gave detailed information on the levels of a number of classes of potential contaminants including dioxins, polycyclic hydrocarbons, herbicides, pesticides and heavy metals. All contaminants measured are within acceptable levels in compliance with EU regulations.

Further Information

9. In accordance with the guidelines on substantial equivalence the applicant also submitted data from some studies carried out with DRT's phytosterols. These studies addressed acute toxicity, skin irritation and skin sensitisation. These studies were evaluated as part of the earlier application from Teriaka. No adverse results 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 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 Prima Pharm can be considered to be substantially equivalent to the existing phytosterol ingredient marketed by Teriaka.

12. Prima Pharm should ensure that the labelling of products containing their phytosterols comply with Commission Regulation (EC) 608/2004 concerning the labelling of foods with added phytosterols, and more specifically to Article 2 of this regulation.

December 2005

APPENDIX VIII

Mr A Klepsch
European Commission
DG-SANCO
Rue De La Loi 200
Brussels
Belgium B-1049

2 December 2005 Reference: NFU 545

Dear Mr Klepsch,

Application under (EC) 258/97 for the novel food ingredient alpha-cyclodextrin (Bioresco, on behalf of Wacker Chemie GmbH)

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 Belgium CA for the above product. This was discussed at the Committee's meeting on 24 November 2005.

The Committee was unable to agree with the positive opinion of the Belgium CA and concluded that additional information is required before the assessment of the safety of this product can be concluded. Members highlighted the following issues as requiring additional clarification:

1. Members noted that diabetics are a group of sensitive consumers requiring special consideration for any novel carbohydrate ingredient. The applicant cites only two studies on page 65 of the application dossier, which indicates that reduced urinary glucose excretion was observed in diabetics after supplementation of the diet with 50g alpha-cyclodextrin. This study by von Hoesslin & Prongsheim (1927) was carried out on two type 1 diabetics and the Committee considered that additional evidence is required to determine the effect of the novel ingredient on diabetics.

2. Members requested further clarification of the consumption estimates provided by the applicant. These estimates, based on US food consumption data and the maximum proposed inclusion levels, indicate that the mean and high level consumption of alpha-cyclodextrin to be 11.4 and 19.8 g/day (0.21 and 0.43 g/kg bw/day respectively). However other estimates based on the GEMS/Food "large portion" database indicate that 38g of the novel ingredient could be consumed from a single large portion of one food (bread). This intake is equivalent to 190 grams of bread (4 large slices) containing 5% of the ingredient. Members therefore asked for this apparent inconsistency to be clarified.

3. Members noted that the estimated average consumption by young schoolchildren exceeds that of adults both in absolute terms and by a factor of four when expressed on a per kilogram body weight basis. Despite this no data were cited on the gastrointestinal tolerance of --cyclodextrin by young children. The applicant cites a NOAEL of approximately 10 g /kg /day in the dog. If a cross-species uncertainty factor of 10 is applied this equates to human intake of 1 g/ kg /day, Members noted that this makes no allowance for inter-individual variation in humans yet closely approximates the estimated 90th centile intake (0.96 g /kg /day) anticipated in the youngest children.

4. Current UK advice is that whilst quantification of dietary fibre should be carried out using AOAC methodology, a method that would include alpha-cyclodextrin in the definition of fibre, however any claims attributed to the consumption of fibre should be made for non starch polysaccharides18. The applicant suggests that the novel ingredient will be used as a source of fibre but the Committee notes that this designation may be misleading to the consumer unless there is evidence that alpha-cyclodextrin confers the same nutritional benefits as non-starch polysaccharides found in fruit and vegetables.

5. The Committee wishes to note that the nutritional labelling of alpha-cyclodextrin with respect to energy value should be in line with the Food Labelling Directive 2001/13/EC and the Nutrition Labelling Directive 90/496/EC.

In view of the ACNFP's assessment, the UK Competent Authority cannot support the marketing of this novel food ingredient until these issues have been satisfactorily addressed.

Yours sincerely

[sent by Email]

Dr Sandy Lawrie
Novel Foods, Additives and Supplements Division

APPENDIX IX

Mr A Klepsch
European Commission
DG-SANCO
Rue De La Loi 200
Brussels
Belgium B-1049

24 January 2006 Reference: NFU 174

Dear Mr Klepsch,

Application under (EC) 258/97 for the novel food ingredient Arachidonic Acid Rich Fungal Oil (Suntory Ltd)

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 Dutch CA for the above ingredient obtained from the fungus Mortierella alpina. This was discussed at the Committee's meeting on 24 November 2005.

The Committee agreed with the overall conclusion of the Netherlands but we wish to make the following comments:

1. Neither the application dossiers nor the initial assessment report appear to define a formal specification for the novel ingredient. However, a suitable specification will be needed to accompany any authorisation that might be issued for this novel ingredient. This specification should include a limit for protein content, since this appears to be the basis for the allergenicity assessment.

2. The applicant has estimated that the likely exposure to the novel ingredient will be 75mg per kg body weight per day, which corresponds to 30 mg of arachidonic acid per kg body weight per day. This figure is consistent with the published median levels of arachidonic acid consumed by infants exclusively fed breast milk in Europe. Commission Directive 96/4EC requires that the total level of arachidonic acid, as a percentage of total fat content in infant formula, must not exceed 1%. As the applicant does not propose an upper limit for incorporation of the novel ingredient into infant formula, in practice the use of the NI is limited by the maximum permitted level of 1% for arachidonic acid (as a proportion of total fat) set in directive 91/321/EEC (as amended by Directive Directive 96/4/EC). ACNFP Members therefore wish to highlight that this

could allow for the addition of significantly more of the novel ingredient than described above. This higher level of intake, which we estimate could be as high as 190 mg per kg bodyweight per day of the fungal oil if it provides all of the maximum permitted ARA, would not however present an additional safety concern.

Yours sincerely

[sent by email]

Dr Chris Jones
Novel Foods, Additives and Supplements Division

APPENDIX X

Mr A Klepsch
European Commission
DG-SANCO
Rue De La Loi 200
Brussels
Belgium B-1049

28 January 2005 Reference: NFU 496

Dear Mr Klepsch,

Application under Regulation (EC) 258/97 – Isomaltulose (Südzucker)

Referring to the Commission's letter of 30th November 2004 the Food Standards Agency, as the UK Competent Authority (UK CA), has sought comments from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the German CA.

The product described in this application is very similar to one from Cargill Cerestar, which was assessed in the UK last year and for which a positive initial assessment report was submitted in March 2004. The range of food uses described by Südzucker is however wider and less precise and there is a different labelling proposal.

While the ACNFP agreed with the safety assessment conducted by the German CA, they raised the following points:

i. The Committee noted that the range of proposed products containing isomaltulose intended for the market by the applicant was wider and more vague than in the first application. Members therefore emphasised their previous concern that the use of isomaltulose could result in an overall increase in energy intake due to misinterpretation of any claims made for reduced sweetness or delayed energy release.

ii. In view of the above, the proposed labelling of the product was considered not to be sufficient. The applicant should be reminded of the need to comply with general labelling legislation and ensure that the product does not mislead the consumer, particularly in relation to its energy content. Any claims referring either to reduced sweetness or to the rate of energy release should be accompanied by a statement of the energy equivalence of the novel ingredient with other sugars, presented in a way that cannot be construed as misleading to consumers.

iii. The application dossier implies a role for isomaltulose in low glycaemic index (GI) diets in the dietary management of diabetes. The Committee agreed that it is generally desirable for diabetic diets to have a low GI. However, foods with a high GI are used in some situations to counter hypoglycaemia. Substituting isomaltulose for sucrose may mislead diabetic consumers in this context, unless the patient is aware of the implications of the substitution.

In conclusion, the UK CA agrees with the safety assessment in the initial opinion but we do not think that authorisation can proceed until the labelling issues are resolved. In particular the applicant ought to clarify how diabetics will be adequately informed about the nutritional properties of isomaltulose-containing products. We would also point out that the ACNFP has previously recommended that the introduction of isomaltulose should be accompanied by a post-marketing monitoring scheme to determine the patterns of consumption and to ascertain whether the use of this ingredient leads to any misunderstanding of the energy content of foods in which it is used. We think that this recommendation also needs to be addressed in relation to the current application.

Yours sincerely

[sent by Email]

Dr Sandy Lawrie
Novel Foods, Additives and Supplements Division

APPENDIX XI

Mr A Klepsch
European Commission
DG-SANCO
Rue De La Loi 200
Brussels
Belgium B-1049

31st March 2005 Reference: NFU 555

Dear Mr Klepsch,

Application under (EC) 258/97 to market a plant sterol enriched rice drink (Teriaka)

As the UK competent authority, 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.

Whilst the UK agree with the conclusions of the Finnish assessment report, we would like to note the following:

1. The translation of the Finnish assessment report states that the labelling will include the following statement: "may be less nutritionally inappropriate for pregnant and lactating women and children under age of five years". The products should be labelled in accordance with Article 2(5) of Regulation (EC) 608/2004 which (in English) uses the wording "the product may not be nutritionally appropriate for pregnant and breastfeeding women and children under the age of five years".

Although not directly relevant to the safety assessment of this product the UK also wishes to note:

a) Statement in Annex 1, concerning the specification of the Diminicol® plant sterol ingredient states that the "vegetable oil sterols are GMO free as verified with PCR test". The applicant has provided no details of the PCR tests used to support this statement and as we are not aware of any commercially available sunflower oil obtained from a GM source, we consider this to be a potentially misleading claim.

b) There are no efficacy data that directly attribute the lowering of blood cholesterol to the consumption of this product. However, it seems likely that any effect would be similar to those previously reported for other approved plant sterol enriched drink products.

In conclusion, the UK CA agrees with the Finnish CA that plant sterol enriched rice drink produced by Teriaka should be given a positive opinion, provided that the labelling of this product is in accordance with Regulation (EC) 608/2004.

Yours sincerely

[Sent by Email]

Dr Sandy Lawrie
Novel Foods, Additives and Supplements Division

APPENDIX XII

Mr A Klepsch
European Commission
DG-SANCO
Rue De La Loi 200
Brussels
Belgium B-1049

13 October 2005 Reference: NFU 518

Dear Mr Klepsch,

Application under (EC) 258/97 for the novel food ingredient Zeaxanthin (Bioresco, on behalf of DSM Nutritional Products)

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 Dutch CA for the above product, at the Committee's meeting on 29 September 2005.

The UK agrees with the conclusions of the Dutch CA that an additional assessment of zeaxanthin is required because the applicant has not provided information on intended products and levels of incorporation. We would also like to highlight the following points for consideration in an additional assessment by EFSA:

1. Whilst the Committee noted that the stability data for zeaxanthin showed that it was stable in a range of food matrices, there was nevertheless measurable degradation during the shelf life of the products. Members suggested that the shelf life should be limited in order to avoid significant reduction in the quantity of zeaxanthin present in the consumed product.

2. Members noted that the applicant had not considered whether there were particular "at risk" groups of the population including those who, as a result of the perceived health benefits attributed to the consumption of this novel ingredient, could be particularly high consumers. Members highlighted elderly people as likely high level consumers and suggested that special consideration be given to this user group.

3. The Committee noted that the study cited on pages 72-76 of the dossier found no crystal formation in the eyes of animals given high doses of zeaxanthin, but it revealed unexpected findings described as "polarising structures". The Committee requested that this issue be evaluated further to determine whether there are implications, especially for the high user group described in point 2.

In conclusion, the UK CA agrees with the initial assessment report from the Netherlands that the assessment cannot be completed without information relating to the intended uses and we ask that the points raised above be taken into account in the further assessment of this application.

Yours sincerely

[Sent by Email]

Dr Sandy Lawrie
Novel Foods, Additives and Supplements Division

APPENDIX XIII

Noni juice notifications

Date of Notification	Notifier	Product	Opinion prepared by
28 January 2005	Resort Health Products	Noni juice	France
11 January 2005	Herbex Ltd. (part of Pacific Islands Noni Association –PINA)	Noni juice	UK *(See 2004 ACNFP annual report)*
15 April 2005	Royal Noni (Fiji) Limited (part of PINA)	Noni juice	UK *(See 2004 ACNFP annual report)*
2 June 2005	Sunline Noni Ltd. (part of PINA)	Noni juice	UK *(See 2004 ACNFP annual report)*
25 May 2005	C.C.K. Trading Ltd. (part of PINA)	Noni juice	UK *(See 2004 ACNFP annual report)*
29 September 2005	Cook Islands Noni (part of PINA)	Noni juice	UK *(See 2004 ACNFP annual report)*
Dated 14 September 2004 (wrongly addressed, therefore received only on 2 May 2005)	Trisana GmbH	Noni juice	Germany
28 June 2005	Mi GmbH	Noni juice	UK *(See section 2.1)*
19 May 2005	NCT Nord Trading GmbH	Noni juice	Germany
27 September 2005	Dynamic Health Laboratories Inc.	Noni juice	Germany

APPENDIX XIV

Phytosterol notifications

Date of notification	Notifier	Product	Opinion prepared by
7 June 2004	Gutierrez Corporaction Alimentaria PEÑASANTA S.A.	Milk type and fermented milk type products. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of phytosterols/phytostanols.	Spain
1 July 2004 4 October 2004	Teriaka Ltd*19	Milk type products and soya drinks. Fermented milk products. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of phytosterols/phytostanols.	Finland
22 July 2004*	Novandie	Yoghurt type products with added phytosterol esters. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterol esters; a container of beverages will not contain more than 3 g of added phytosterol esters	Directly to the Commission (The phytosterol ingredient is the one that was notified by Cognis)

*Notifications complement the authorisations previously granted to these companies for the use of phytosterols in other food types.

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
23 July 2004 20 April 2005	Cognis	Milk type products. Yoghurt type products; yellow fat spreads as described by Council Regulation (EC) N° 2991/94. Yellow fat spreads, salad dressings including mayonnaise and milk type products as specified by Commission Decision 2004/333/EC, spicy sauces as specified by Commission Decision 2004/334/EC and milk based fruit drinks as specified by Commission Decision 2004/336/EC. The requirements laid down in Article 2 of the aforementioned Decisions applies.	UK Finland
29 July 2004	Danone	Yoghurt. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of phytosterols/phytostanols.	Finland
30 August 2004	LÁCTEAS GARCIA BAQUERO S.A.	Cheese with added phytosterols. The cheese type products shall be presented in conformity with the provisions of Article 2 of the relevant Commission Decisions.	Ireland
30 August 2004	Dairygold	Yellow fat spreads excluding cooking and frying fats and spreads based on butter or other animal fat with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterol esters.	Ireland

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
30 September 2004	LACTOGAL	Milk and yoghurt type products. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterol esters; a container of beverages will not contain more than 3 g of added phytosterol esters	Directly to the Commission (The phytosterol ingredient is the one that was notified by Cognis)
24 October 2004	Cargill	Yellow fat spreads; Salad dressings, mayonnaise and spicy sauces; Milk-type drinks with fruit and/or cereals, milk-based fruit drinks, fermented milk type products, and soy drinks; Cheese type products. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of added phytosterols/phytostanols.	Finland
23 November 2004	Danone Vitapole for Compagnie Gervais Danone	Fermented milk type products with added phytosterol esters. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterol esters; a container of beverages will not contain more than 3 g of added phytosterol esters	Finland (The phytosterol esters ingredient is the one that was notified by Cognis)
22 April 2005	Forbes Medi-Tech Inc.*	Foods listed in Article 1 of Commission Decision 2000/500/EC and in annex 1 of Commission Decisions 2004/333/EC, 2004/334/EC, 2004/335/EC and 2004/336/EC (yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks, cheese type products, yoghurt type products, spicy sauces, milk based fruit drinks) with added plant sterol esters	Finland

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
22 April 2005	Forbes Medi-Tech Inc*	Foods listed in Article 1 of Commission Decision 2000/500/EC and in annex 1 of Commission Decisions 2004/333/EC, 2004/334/EC, 2004/335/EC and 2004/336/EC (yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks, cheese type products, yoghurt type products, spicy sauces, milk based fruit drinks) with added phytosterols/phytostanols (Phyto-S-SterolsTM)	Finland
22 April 2005	Forbes-Medi-Tech*	Yellow fat spreads, salad dressings, fermented milk type products, soya drinks, cheese type products, yoghurt type products, spicy sauces, milk based fruit drinks	Finland
10 May 2005	Juustoportti Oy	Yoghurt type products with added phytosterols/phytostanols (Reducol™). The yoghurt type products shall be presented in conformity with the provisions of Article 2 of Commission Decisions 2004/334/EC – 2004/336/EC	Finland
10 May 2005*	Juustoportti Oy	Yoghurt type products with added phytosterols A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of added phytosterols	Directly to Commission
10 May 2005	Juustoportti Oy	Yoghurt type products	Finland

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
11 May 2005	ELSA Estavayer	Milk type and yoghurt type products with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterol esters; a container of beverages will not contain more than 3 g of added phytosterol esters	Directly to the Commission (The phytosterol esters ingredient is the one that was notified by Cognis)
27 May 2005	Novandie	Yoghurt type products and other dairy products with added phytosterol esters (ReducolTM). The yoghurt type products and other diary products shall be presented in conformity with the provisions of Article 2 of Commission Decision 2004/845/EC.	Germany
30 May 2005*	MIFA AG	Yellow fat spreads with added phytosterol esters. The yellow fat spreads shall be presented in conformity with the provisions of Article 2 of the relevant Commission Decisions.	Directly to the Commission (The phytosterol esters ingredient is the one that was notified by Cognis)
17 June 2005*	Pingo Doce Distribuição Alimentar S.A.	Milk based beverages with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of added phytosterols.	Directly to Commission

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
27 June 2005*	Robert Wisemans & Sons Limited	Milk based beverages with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of added phytosterols.	Directly to Commission
5 July 2005*	Kerry Foods	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. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols.	Directly to Commission
5 July 2005	Homann Feinkost	Salad dressings and mayonnaises with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; the foods will be packed as single portions.	Finland

*This was technical notification where the "novel" product is accepted on the basis that the applicant company intends to market *exactly* the same phytosterol ingredient that has already been approved under Regulation (EC) No 258/97.

Phytosterol notifications *(continued)*

Date of notification	Notifier	Product	Opinion prepared by
13 July 2005	Fayrefield Foods Ltd.	Yellow fat spreads with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols.	Ireland
5 August 2005*	Granarolo S.p.a.	Fermented milk (yoghurt) type products with added phytosterols. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of phytosterols/phytostanols.	Commission
26 August 2005	Skånemejerier	Yoghurt type products. A portion will not contain more than 3 g (in case of one portion per day) or more than 1 g (in case of 3 portions per day) of added phytosterols/phytostanols; a container of beverages will not contain more than 3 g of phytosterols/phytostanols.	Directly to the Commission
2 September 2005*	Nöm AG	Milk type products with added phytosterols. The milk type products shall be presented in conformity with the provisions of Article 2 of the relevant Commission Decisions	Directly to the Commission (The phytosterol esters ingredient is the one that was notified by Cognis)
27 September 2005	Degussa Food	Foods listed in annex 1 of Commission Decisions 2004/333/EC, 2004/334/EC, 2004/335/EC and 2004/336/EC (yellow fat spreads, salad dressings, milk type products, fermented milk type products, soya drinks, cheese type products, yoghurt type products, spicy sauces, milk based fruit drinks) with added plant sterol esters	Finland

APPENDIX XV

STATEMENT ON THE EFFECT OF GM SOYA ON NEWBORN RATS

The Committee has examined a report provided to it by Dr Irina Ermakova containing preliminary results from a study of genetically modified (herbicide-tolerant) soya that was conducted in Russia. The report described reduced growth and increased mortality amongst pups born to rats given soya flour from GM soya beans, when compared with those born to rats given non-GM soya flour or a control group given no soya.

The report lacks detail essential to meaningful assessment of the results. In particular, it does not provide key information concerning the composition and nutritional adequacy of the test diets. Also, the Committee notes that these are preliminary results; the study has not been quality-controlled through the normal peer review process preceding scientific publication.

It is well known that rodents fed large quantities of raw soya will suffer various nutrient imbalances that cause reduced growth rates and other adverse effects. This would be expected whether the soya beans are from a GM or non-GM source. It is also well known that protein quality varies between varieties and geographical origins of soya, independently of whether they have been genetically modified. It is therefore essential to ensure that diets which contain a high proportion of different types of soya are carefully balanced and equivalent in terms of nutrients and anti-nutritional components. It is not known whether this was done in the present study.

Unusually, the soya flour was given to the animals alongside conventional feed pellets rather than incorporated into the feed. The mothers received up to 20g of soya flour per day during the study, which could have displaced a significant quantity of the conventional feed pellets which normally assure optimum vitamin and mineral intake. The quantities of soya consumed by each animal are not known and there are no data on the consumption of the conventional feed. Neither were any data on cause of death provided.

The GM and non-GM soya samples were obtained from different sources and there is no information on the presence of potential contaminants, such as mycotoxins, resulting from contamination during transportation and storage.

In conclusion, there are a number of possible explanations for the results obtained in this preliminary study, apart from the GM and non-GM origin of the test materials. Without information on a range of important factors conclusions cannot be drawn from this work. The Committee Secretariat is contacting Dr Ermakova to obtain further information on this study and the Committee will consider any further information that can be obtained and review the position if a full report of the study is published in the peer-reviewed literature.

The Committee also notes that Dr Ermakova's findings are not consistent with those described in a peer-reviewed paper published in 2004.[19] In a well controlled study no adverse effects were found in mice fed on diets containing 21% GM herbicide-resistant soya beans and followed through up to 4 generations.

[19] "A generational study of glyphosate-tolerant soybeans on mouse fetal, postnatal, pubertal and adult testicular development" Brake DG ane Evenson DP, Food and Chemical Toxicology 42 (2004) 29-36.

APPENDIX XVI

Suzy Renckens
Secretary, GMO Panel
EFSA
Largo N. Palli 5/A
I-43100 Parma
Italy

3 October 2005 Reference: NFU 526

Dear Dr Renckens

Draft guidance document for the risk assessment of genetically modified microorganisms and their derived products intended for food and feed use

I would like to submit the following comments on behalf of the UK Competent Authorities for GM food and feed, which we have assembled after consulting the relevant UK advisory committees dealing with novel foods and processes (ACNFP) and releases into the environment (ACRE).

General comments

The guidance is comprehensive and is largely consistent with the existing guidance for GM plants. However, the document is very highly structured, implying a common approach to dossier production for the wide range of possible products containing, or derived from, GMMs. We are a little wary of that implication, and would, perhaps, have liked to see more about the EFSA requirements and less detail about how precisely they might be met.

Due to the lack of experience with the risk assessment of GMMs and derived products, it will be necessary to review the guidelines at periodic intervals to profit from the practical experience gained from such assessments.

Specific comments

Section I p6-11: the guidelines should describe a global approach to the safety assessment of GMMs and all products derived from them rather than be constrained with respect to any particular pieces of legislation (i.e. independently of their legislative status). While the lengthy section I.2 describing Regulations and Directives may reflect the current position, it seems to be of limited relevance to these safety guidelines.

Section I.1 p7 line 2: Although socioeconomic and ethical considerations are outside the scope of the guidance, they are of great concern to some

consumers and should not be dismissed so lightly. We therefore suggest that the guidelines should, as a minimum, acknowledge these concerns before explaining why they are not addressed as part of EFSA's risk assessment process for GMOs.

Section I.1 p7, line 4: The statement that the document does not apply to contained use of GMMs needs to be clarified, since it does cover enzymes and other fermentation products produced by, or extracted from, the contained use of GMMs. The guidelines should also clarify the position with respect to all fungi (as these range from yeasts and organisms such as Aspergillus sp., already widely used in enzyme production, through to mushrooms and other edible fungi).

Section II: The issue of the transfer of antibiotic resistance markers from GMOs to microorganisms is a major area of concern to the public and this is of even greater relevance in the case of transfer from GMMs to other microorganisms. We therefore suggest that the issue is specifically discussed in Section II, including a comparison of the relative probability of gene transfer from GMMs and from GM plants, in order to support and explain the recommendation about the use of ARMs on p16. On page 15 (line 16) the bullet point should read, "the potential for gene transfer and selection of the transgene, including any selection markers";

Section II.3 p14 line 30-32: this sentence should be expanded to include gene loss and gene duplication, in addition to gene order and expression. Both of these can be a consequence of the manipulations involved in chromosomal manipulations, and are easily detectable if whole genome arrays are available.

Section II.7 p16 line19: If profiling technologies are to be used for the assessment of GMMs, careful consideration will need to be given to the experimental conditions chosen. The response of GMMs to conditions in vitro – for example in standard shake flask experiments in rich medium – is likely to be unrepresentative of their behaviour in real situations, for example in foods or in the human or animal gut.

Section IIIC.2.b, p29-30: We agree that the methods used to remove and/or kill live GMMs will be a critical factor in the assessment and each applicant will need to demonstrate that methods used, and the detection method used to provide confirmation, are appropriate for the organism in question. In particular, the problem of viable but non-culturable organisms needs to be addressed, since it is well established that estimates of viable counts can be very significantly distorted (by several orders of magnitude) by the methods chosen for cultivation.

Section IIIB.1.7 p19 line 34: The guidance should be more specific about the methods used to ensure the reproducibility and statistical significance of the data generated in the required studies. The reference only to "within-laboratory validation" (line 35) should be replaced by "validation within the laboratory or, preferably, between laboratories".

Section IIIC.6: As with the current GM plant guidelines, the discussion on allergenicity is limited to IgE mediated reactions but this is not the only mechanism for individuals to have adverse reactions to food. Also, substances present in food may modulate immune responses without themselves being allergens. The GMO Panel has recently established a self-tasking activity on the allergenicity assessment of GM foods and it might be useful for this group to consider whether the scope of the current allergenicity assessment (of GM and other novel foods and ingredients) needs to be expanded to include wider aspects of immunogenicity.

Section IIIC.6.10 p41 line 5: the reference to Wal et al (2003) is inappropriate since it relates to post-market monitoring of pharmaceuticals. Specifically, it is misleading to imply that post-market monitoring of foods might be needed to check for expected side-effects.

I hope these comments are clear and of use to the GMO Panel.

Yours sincerely

[Sent by Email]

Dr Sandy Lawrie
Novel Foods, Additives and Supplements Division

APPENDIX XVII

Mr Robert Vint
Director, Genetic Food Alert
Hope House
75a High Street
Totnes
TO9 5PB

13 June 2005 NFU 13

Dear Mr Vint

GM FOOD SAFETY RESEARCH

Thank you for your letter of 6 December regarding the use of animal studies in the safety assessment of GM foods. As described previously by the ACNFP Secretariat, your letter was discussed by the Committee at its meeting on 26 January. I apologise for the lengthy delay in replying to you. This was due to an oversight by the Committee Secretariat, coupled with the fact that staff in the relevant part of the Food Standards Agency were diverted to deal with other urgent food safety incidents.

In your letter you questioned why research on the safety of GM foods has not been carried out on humans and animals, referring to a number of recent papers published in the British Journal of Nutrition and in the Journal of Nutrition reporting the effects of whole foods in animal feeding studies and in human studies.

In January, Committee members noted that feeding trials are an important tool under specific circumstances but re-iterated that there is no scientific justification for insisting that novel foods (including GM foods) should routinely be tested in this way. In some cases, feeding trials are in fact carried out in laboratory or farm animals by the company that has developed a GM crop. These are normally designed to test the precise nutritional qualities of the crop (e.g. maize grain) when used as a major part of an animal's diet, as small differences in feed efficiency can be of considerable economic importance to the animal feed industry. The Committee's view is that these studies may provide some limited confirmation that that foods derived from these crops are not overtly toxic, but they do not provide evidence of safety.

The papers highlighted in your letter reported on studies that were conducted to test specific hypotheses concerning the effects of the relevant foods and food ingredients. It would be reasonable to conduct similar studies in the case where a novel or GM food is plausibly anticipated to have a specific biochemical effect that is relevant to human health.

It has been accepted since the earliest discussions on testing of "whole" foods that feeding trials with novel and GM foods are not a practical way of gathering evidence of their general safety. Instead, the safety evaluation focuses on detailed examination of the observed differences between the novel or GM food and its existing counterparts – for example by isolating novel constituents and testing them at high doses in animal models.

This approach has been confirmed at various times following reviews of the procedures for safety assessment of novel or GM foods. You may be interested to know that the value of animal feeding trials is currently being re-examined by the GMO Panel of the European Food Safety Authority, which is now responsible for GM food safety assessments in the European Union.

The ACNFP is not able to comment on other issues raised in your letter, such as the reference to campaigns to intimidate or ridicule scientists who have raised concerns over the safety of GM food or the suggestion that the Government has decided on a moratorium on safety research until GM foods are on the shelves.

Yours sincerely

Professor Mike Gasson
ACNFP Chairman

Cumulative Index

Published by Food Standards Agency
June 2006
FSA/1065/0506