The Advisory Committee on Novel Foods and Processes (ACNFP)

2011 Report

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NOVEL FOOD APPLICATIONS SUBMITTED TO THE UK

(a) Full applications

In 2011 the ACNFP considered three new applications under Article 4 of regulation (EC) 258/97. These are detailed in Table 1, below. Details of the issues that were raised by the Committee can be found in the Minutes of the relevant meetings (Annex 2). The Committee concluded its assessment of two of these applications during this calendar year and also completed its assessment of three applications which were carried over from previous years.

Table 1: Novel food applications made via the UK that were considered by the Committee during 2011

Novel food (Applicant)	***Meeting discussed***	***Initial opinion***	***Comment***
Dihydrocapsiate (Ajinomoto)	Feb	Completed Annex 3(a)	Positive initial opinion was issued in February 2011
Taxifolin (Ametis JSC)	Feb, May	Completed Annex 3(b)	Positive initial opinion was issued in February 2011
Phosphated Distarch Phosphate (MGP Ingredients)	May	Completed Annex 3(c)	Positive initial opinion was issued in August 2011
Rooster Comb Extract	Feb, May	Completed Annex 3(d)	Positive initial opinion was issued in October 2011
DHA and EPA Rich Algal Oil (Martek Bioscience)	Feb, May, Nov	Completed Annex 3(e)	Positive initial opinion was issued in December2011
Chia Seed (extension of use) (The Chia Company)	Feb, Sept (postal)	-	Positive initial opinion issued in 2012

(b) Opinions on substantial equivalence

In 2011 the ACNFP considered one request for an opinion on equivalence in accordance with Article 3(4) of regulation (EC) 258/97. This is detailed in Table 2, below. Details of the issues that were raised by the Committee can be found in the Minutes of the relevant meeting (Annex 2). The ACNFP did not conclude its assessment of this request during this calendar year.

Table 2: Applications for an opinion on substantial equivalence that were considered by the Committee during 2011

Novel food (Applicant)	*Meeting discussed*	*ACNFP Opinion*	*Comment*
DHA Rich Algal Oil (Ocean Nutrition)	Nov	Pending	Opinion issued in 2012

NOVEL FOOD APPLICATIONS SUBMITTED TO OTHER MEMBER STATES

In 2011 the ACNFP considered five initial opinions from other EU Member States. These are detailed in Table 3, below. The ACNFP's advice formed the basis of the UK's comments or objections to the marketing of these novel foods. Details of the issues that were raised by the Committee can be found in the Minutes of the relevant meeting and in the responses sent to the European Commission.

Table 3: Novel foods considered by the Committee during 2011 following an initial assessment in another Member State

Novel food (Member State)	*Meeting discussed*	*UK response*	*Comment*
Synthetic Chewing Gum Base (Netherlands)	Sept	Annex 3 (f)	Objections (effects on gut flora)
Krill Oil(extension of use) (Finland)	Sept	Annex 3 (g)	Minor comments
Coriander Seed Oil (Ireland	Nov	Annex 3 (h)	Objections (concerns about metabolism of petroselenic acid and protein assay employed)
Synthetic Vitamin K2 (Germany)	Nov (Postal)	Annex 3 (i)	Comments
Gamma amino butyric acid (Ireland)	Sept (postal)	Annex 3 (j)	Objections (poorly characterised; potential for neurological effect, 13 week toxicological study is poorly designed)

NOVEL FOOD APPLCIATIONS CONSIDERED IN PREVIOUS YEARS

During 2011 the ACNFP also considered a response from an applicant company, and an opinion from the European Food Safety Authority (EFSA) which following reasoned objections to the marketing of novel foods (Article 6(4) of regulation (EC) 258/97). These are detailed in Table 4, below. Details of the issues that were raised by the Committee can be found in the Minutes of the relevant meeting

Table 4: Novel foods considered by the Committee during 2011 following an initial assessment in another Member State

Applicant response or EFSA opinion	***Meeting discussed***	***Comment***
Gamma Cyclo Dextrin (Response)	Feb, Sept	Objections sustained (concerns that gamma-cyclodextrin might interfere with the absorption of fat-soluble vitamins, particularly vitamin D. Issue subsequently addressed(refer to 2012 report)
Liquorice Root Extract (EFSA)	Sept	Objections previously addressed

OTHER ISSUES

In 2011 the ACNFP also considered a number of other issues which related to novel foods, nanotechnology, GM plants and the functioning of the Committee. These are detailed in Table 5, below.

Table 5 Other Issues	***Meeting discussed***	***Comment***
EFSA GM Plant Comparators (draft)	Feb (Postal)	Combined UK response submitted online (ACNFP and ACRE). In general ACNFP and ACRE considered that the EFSA draft document on GM plant comparators was practical and proportionate; but drew attention to issues concerning the introduction of deliberate compositional changes, the effects of backcrossing and approaches to the risk assessment of (1) GM plants transformed with multiple genes and (2) stacked events
EFSA Guidance on risk assessment of GM microorganisms	Feb (postal)	ACNFP comments submitted online. In general the ACNFP found that the draft EFSA guidance for the assessment of GMMs is very thorough, well written, and easy to follow; but

(updated)		highlighted issues related to the allergenicity, nutritional profiling, processing and alteration of endogenous gene expression of GMMs, as well as the absence of any mention of the influence of genetic modification on epigenetic effects
EFSA Guidance on risk assessment nanoscience and nanotechnologies to food and feed (draft)	Feb	The Committee also advised that the proposed framework should not be too prescriptive, as it may become rapidly outdated. The Committee was concerned there was no reference to allergenicity of nanomaterials derived from proteins as there is evidence that the physical form of a protein may affect its digestibility and its allergenic potential. See Annex 3(k)
EFSA draft guidance on the risk assessment of food and feed from GM animals	Sept	ACNFP comments submitted online. The ACNFP was of the opinion that the guidance focuses too much on adapting the requirements for GM plants when a fresh approach would probably be more beneficial. The emphasis should be on the general principles for the risk assessment of GM animals and the methods to be used, perhaps with some specific examples of how particular issues might be handled. The use and production of GM animals is a fast-moving area and flexibility is essential. Further detailed comments on specific points were also addressed.
EFSA draft guidance on repeat dose oral toxicity studies	Sept (Postal)	Guidance should take account of physiochemical properties of diets which are likely to differ between whole foods and purified diets, need for "balancing" of the control and test diets to take account of differing nutritional effects, guidance on the choice of comparator or control for the test product needed (Refer to minute Annex for detail)
ACNFP Guidance for low level protein analysis	Feb	Completed http://acnfp.food.gov.uk/acnfppapers/inforelatass /proteinsinnovelfood/
Under Reporting in the National Diet and Nutrition Survey (NDNS)	Sept	Increased post market monitoring where there was uncertainty about consumption of relevant foods by specific groups of the population, margins of safety were unclear when "child-friendly" foods were targeted by manufacturers, cumulative exposure to novel foods with similar effects was difficult to address. NDNS data might be strengthened by using biomarkers to confirm the completeness of food diaries

Novel sources of selenium and zinc. (two EFSA opinions)	May	The Committee was asked to note that zinc L-pidolate has previously been cleared by EFSA as a source of zinc and that selenitetriglycerides will be evaluated in due course by EFSA as a source of selenium. As the Committee highlighted the need to assess the bioavailability of this new source of selenium and whether this formulation with triglycerides altered its distribution and accumulation within the body, for example in adipose tissue. See Annex 3(l)
Proposal to replace the Novel food Regulation (Update)	May	Noted
ACNFP Advice	Sept	Summary of advice given to the FSA between 2005 and 09 and subsequent actions taken (refer to paper ACNFP/103/5)

Annex 1 – Information about the Committee

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.

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 2011, 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 2011 and a copy of the code of conduct for ACNFP members can be found on the following pages.

Membership of the Committee during 2011

Chairman

Professor Peter Gregory BSc, PhD

Chief Executive of the Scottish Crop Research Institute, Chief Executive of East Malling Research and Professor of Global Food Security at the University of Reading.

Members

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

Professor Michael Bushell BSc, PhD (Microbiologist)
Professor of Microbiology and Head of Microbial Sciences at the University of Surrey.

Professor Andrew Chesson BSc, MSc, PhD, CChem, FRSC (Nutritionist)
Independent Scientific Adviser and Honorary Professor at the University of Aberdeen.

Jayam Dalal (Consumer affairs)
Freelance marketing consultant and Independent Public Appointments Assessor accredited by the Office of the Commissioner for Public Appointments.

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

Professor Paul Haggarty BSc, PhD (Nutritionist)
Head of Nutrition & Epigenetics and Senior Lecturer, Rowett Institute of Nutrition and Health, University of Aberdeen and Honorary Clinical Scientist in Grampian NHS Trust.

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.

Professor John Mathers BSc, Dip. Nutr, PhD (Nutritionist)

Professor of Human Nutrition and Director of the Human Nutrition Research Centre at Newcastle University

Professor Peter Meyer BSc, PhD (Molecular Biologist)

Professor of Plant Genetics, The University of Leeds

Professor Clare Mills BSc, PhD (Plant science and allergy expert)
Head of the Structuring Food for Health Programme at the Institute of Food Research in Norwich and Professor of Molecular Allergology, at the School of Translational Medicine, University of Manchester.

Gillian Pope (Consumer affairs)
Company Secretary for NRC (Europe) Ltd.

Professor Christopher Ritson BA, MAgrSc (Expert in Ethics)
Professor of Agricultural Marketing and former Dean of the Faculty of Agriculture and Biological Sciences at Newcastle University.

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

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

FSA Assessors

Mr T Donohoe	Food Standards Agency
Ms H Neathey	Food Standards Agency (Wales)
Ms A Taylor	Food Standards Agency (Scotland)
Mr G McCurdy	Food Standards Agency (Northern Ireland)

ACNFP Members' Interests during 2010

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor Peter Gregory	East Malling Research	Chief Executive	None	
	Royal Horticultural Society	Trustee		
	Produced in Kent	Non-Exec Director		
	Rank Prize Nutrition Committee	Member		
	Informal Research Advisory Group	Member		
	Dfid			
Dr Paul Brantom	Advisory Committee on Animal Feedingstuffs (ACAF).	Committee Member	None	
	Expert Committee on Pesticide Residues in Food (PRiF).			
Professor Michael Bushell	Abbott Laboratories Chicago	Consultant	None	
Professor Andrew Chesson	None	None	European Food Safety Authority	Chair of FEEDAP panel and member of Scientific Committee

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
Jayam Dalal	Agricultural Wages Committee.	Vice Chair.		
Professor Harry Flint	Shell.	Shareholder.	Provexis Alizyme.	Research funding.
	Syral.	Member of Scientific Advisory Board		
Dr Paul Haggarty	Smith Nephew	Shareholder	Pharmaton	Unpaid advisor on pregnancy study protocol.
	Diageo	Shareholder		
	Cafe Direct	Shareholder	Editorial consultant on the American College of Physicians' Information and Education Resource	Consultation fee contributed to research funds.
			Nutrition and Health Conference and German Society for Reproductive medicine	Lecture fees contributed to research funds.

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor Stephen Holgate	Merck Research Laboratories and MSD Novartis. Laboratorias Almirall. Amgen. Synairgen (Spin out company University of Southampton).	Consultant.	Novartis. MSD.	Research Funding.
	Synairgen.	Shareholder/ Director.	Various charities and trusts.	Trustee.
	Southampton Asset Management.	Director.	Advisory Committee on Hazardous Substances	Chair

Personal Interests			Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor John Mathers	None		EU	Research funding
			BBRSC	Research funding
			MRC	Research funding
			Governing Council of the British Nutrition Foundation	Member
			Lifelong Health and well being Research Advisory Panel	Member
			BBRSC DRINC Advisory Panel	Member
Professor Peter Meyer	None		None	

Personal Interests			Non-personal Interests	
Member	Company	Interest	Company	Interest
Professor Clare Mills			FSA.	Occasional External reviewer. PI on FSA funded project T07062. CoI on FSA funded TEXTFALL
			BBSRC	Member of DRINC steering group Core member Committee C
			EU funded research	CHANCE project
			University of Nebraska Food Allergy Research and Resource Programme, USA	Joint PhD student : collaborations on databasing (informaAll)
			Industry : Novartis DBV	
			Neogen Corp	Provision of challenge meals for diagnosis of food allergy
			Exponent Pepsico	Protein purification expert advice

Personal Interests			Non-personal Interests	
Member	Company	Interest	Company	Interest
Mrs Gillian Pope	None		None	
Professor Chris Ritson	Home Grown Cereals Authority	Deputy Chairman (June 2000-March 2008)	Food Ethics Council Cereals Industry Forum EU	Director/Trustee Chairman Research Funding
Professor Peter Shewry	Journal of Cereal Science Various Various Association of Applied Biologists	Reviews Editor Occasional laboratory review panel member Editors and other royalties Vice President	EU Fra FSA Rank Prize Funds Alpro Foundation	Funded research Funded research Funded research Trustee Member of Advisory Committee UK
Professor John Warner	UCB Pharma Ltd.	Chairman of Scientific Advisory Board.	Danone UCB Pharma. Food & Drink Federation.	Funded Research

	Personal Interests		Non-personal Interests	
Member	Company	Interest	Company	Interest
	Merck.	Member of Scientific Advisory Board.	Anaphylaxis Campaign.	Trustee
	Danone	Member of Scientific Advisory Board Research Funding		
	Novartis	Scientific Advisory Board		
	Allergy Therapeutics	Scientific Advisory Board		

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 31);

- 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 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.

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 33 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.

Different types of interest

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

Personal Interests

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

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

Non-Personal Interests

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

- **Fellowships**: the holding of a fellowship endowed by industry or other relevant body;
- **Support by Industry or other relevant bodies**: any payment, other support or sponsorship which does not convey any pecuniary or material benefit to a member personally, but which does benefit their position or department e.g.:

(i) a grant for the running of a unit or department for which a member is responsible;

(ii) a grant or fellowship or other payment to sponsor a post or a member of staff or a post graduate research programme in the unit for which a member is responsible (this does not include financial assistance for undergraduate students);

(iii) the commissioning of research or other work by, or advice from, staff who work in a unit for which a member is responsible.

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

Trusteeships: any investment in industry held by a charity for which a member is a trustee. Where a member is a trustee of a charity with investments in industry, the Secretariat can agree with the member a general declaration to cover this interest rather than draw up a detailed portfolio.

Definitions

For the purposes of the ACNFP 'industry' means:

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

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

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

GOOD PRACTICE GUIDELINES FOR THE INDEPENDENT SCIENTIFIC ADVISORY COMMITTEES

PREAMBLE

Guidelines 2000: Scientific Advice and Policy Making1 set out the basic principles which government departments should follow in assembling and using scientific advice, thus:

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

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

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

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

[1] Guidelines on Scientific Analysis in Policy Making, OST, October 2005. Guidelines 2000: Scientific advice and policy-making. OST July 2000
[2] Code of Practice for Scientific Advisory Committees, OST December 2001
[3] Report on the Review of Scientific Committees, FSA, March 2002

THE GOOD PRACTICE GUIDELINES

These Guidelines have been developed by 9 advisory committees:

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

These committees share important characteristics. They:

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

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

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

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

Principles

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

Defining the issue

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

Seeking input

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

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

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

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

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

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

Validation

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

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

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

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

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

    - whether stakeholders can provide unpublished data.

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

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

Uncertainty

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

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

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

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

Drawing conclusions

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

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

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

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

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

Communicating committees' conclusions

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

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

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

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

reasons will be clearly set out, explained and a commitment made to future publication wherever possible.

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

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

Financial Statement

ACNFP is an independent SAC, but does not have resources of its own. The operation of the Committee is funded by the FSA. In the period of this report, costs for this support (covering Members expenses and fees and administrative cost for the meetings) were £23,602

(a) Minutes of 101st meeting (Feb 2011)

1. Minutes of the 100th meeting — DRAFT/ACNFP/100/Min

The Committee agreed the minutes were a true record of the 100th meeting of the ACNFP held on Thursday 25 November 2010.

2. Matters Arising and Postal Consultations

The Secretariat reported back on matters arising from the 100th meeting. The outcome of two postal consultations undertaken during December and January were summarized. The two consultations were:

- EFSA Draft Guidance on GM plant comparators (postal paper ACNFP/101P/1)
- EFSA Updated Guidance on risk assessment of GM microorganisms and their food and feed (postal paper ANFP/101/P/2).

The comments received from Committee Members had been collated and fed in to EFSA as part of the UK's response to these consultations.

3. Under-reporting in the National Diet and Nutrition Survey (NDNS) ACNFP/101/1

Dr Tedstone from the Department of Health's Nutrition Division introduced this item. The question of intake estimation had been raised in a previous ACNFP meeting in the course of a novel food evaluation, where it was pointed out that estimates prepared on the basis of data from the National Diet and Nutrition Survey (NDNS) could be inaccurate, as there is significant under-reporting of food consumption in this type of survey.

The question of under-reporting was identified some time ago in the nutrition area, and studies had shown that the energy content of an individual's reported diet did not correspond to energy expenditure as measured by other means (doubly-labelled water). However, attempting to make corrections to the data would lead to more uncertainty.

The Committee thanked the Department of Health for their useful paper.

A European wide survey is not close to being undertaken. The data collected by the European Food Safety Authority is variable. Data from a nutrition survey at a European level would not be useful as different countries have different levels of resources.

The Department of Health reported that habitual intake levels differed from intake levels over a period of 7 days. Consumption of some foods may also be under-reported as a result of lack of capture depending on the number of days of the week the survey is undertaken. Mis-reporting also occurs in ethnobiological studies where data is poorer than for a national survey.

The Committee considered whether there should be more post market monitoring on novel foods, in cases where thrre was uncertainty about the way that certain ingredients or about consumption of relevant foods by specific groups of the population, such as children and teenagers. The Committee was concerned that adequate margins of safety were unclear when "child-friendly" foods were targeted by manufacturers producing novel carbohydrate rich snack foods and also that the issue of cumulative exposure to novel foods with similar effects was difficult to address. The DH officials advised there was less under-reporting in children and more in adolescents, and agreed with the Committee that it was difficult to determine margins of safety properly for example because portion sizes differ.

The Committee considered that the NDNS data might be strengthened by using biomarkers to confirm the completeness of food diaries. DH reported that the NDNS is looking at biomarkers but that more work was needed and they would not be used in the near future

4. Synthetic Dihydrocapsiate **(oral report)**

The Committee considered this application in September and November 2010. The Committee was given an oral update on the public consultation on the initial opinion, which had not raised any new issues. It was content that the assessment of this novel ingredient was complete and a favourable UK initial opinion would be forwarded to the European Commission.

5. Taxifolin **ACNFP/101/3**

The Committee considered this application in September and November 2010. The Committee was asked to consider comments from the public consultation on this application before finalising its opinion.

In the light of a previous response received by the applicant the Committee raised a general point about the use of non-EU accredited laboratories and whether this could affect the quality and reliability of analytical data.

After considering the public comments, the Committee requested further data on the levels of saponins in the product and how this compares to the saponin content of existing foods such as soya. The Committee also asked about quality control procedures that were employed on each of the batches of the novel ingredient and also whether there were any checks carried out in relation to mycotoxins, as the tree stumps used to obtain the novel ingredient might subject to fungal decay. Members agreed various amendments to the text of its draft opinion, subject to resolving these remaining issues.

6. Gamma-cyclodextrin **ACNFP101/4**

The Committee considered the Irish Competent Authority's initial opinion on this application for authorisation of gamma-cyclodextrin as a novel food ingredient by postal consultation in September 2010. The Committee was asked to consider the response from the applicant to a number of concerns that had been raised by Members during this consultation.

The Committee noted that its concerns about labelling had not been addressed by the applicant.

The Committee considered that it was difficult to assess the safety of the novel food ingredient with the current state of knowledge. It considered it couldn't make a judgement on whether the ingredient was beneficial or detrimental and it would be necessary to look at dietary survey comparisons. The Committee advised that there was insufficient information to assess the consequences of interactions with lipophillic substances including fat-soluble vitamins. Although the applicant had suggested that the novel ingredient may be useful for diabetics, it has only tested on healthy adults. The Committee also considered that further information was needed about the intended use and expected intake of the novel ingredient. The Secretariat noted the Committee's concerns and reported that the applicant had provided additional information to other Member States which may address some of these.

The Committee was satisfied that its concerns about the intestinal fate of the ingredient had been answered.

7. Phosphated Distarch Phosphate **ACNFP/100/5**

The Committee had considered EFSA's opinion on this application for authorisation of phosphated distarch phosphate as a novel food ingredient, at its previous meeting in February 2011. As differing views were expressed on the mandatory labelling of this novel ingredient, in respect of gastrointestinal effects in children, the Committee was asked to consider whether such a label is necessary.

The Committee agreed with EFSA that resistant starch helps to reverse acute disease states such as cholera and diarrhoea. However, if resistant starch is added to foods there is evidence of laxation in normal individuals. The Committee noted that the studies referenced by EFSA were not of the same starches as the novel ingredient and it was not correct to assume that if one type of resistant starch had no side effects then all the others would be the same. It therefore confirmed that it would be advisable to inform consumers of the potential GI effects of this ingredient and advised that the label might read "may cause altered bowel habits"

8. Rooster Combs Extract **ACNFP/101/05**

The Committee was asked to consider an application from the Spanish company Bioiberica to the UK competent authority for the approval of Rooster *[cockerel]* comb extract rich in sodium hyaluronate as a novel food ingredient.

The Committee was concerned about possible allergic reactions in people who are allergic to egg proteins. The Committee considered it was not to just indicate the possibility of allergic reactions through precautionary labeling and requested the applicant performed more analysis to determine whether antibodies to egg proteins would cross-react with the proteins in the novel ingredient.. The committee also noted that the current rules on allergen labeling refers to hens and therefore may cause confusion if it is applied to a product from cockerels.

The Committee noted that the novel food ingredient was intended for use in a wide range of foods including those available to children. The Committee therefore requested consumption levels of the novel ingredient for both children and adults. The Committee also requested justification of the applicant's approach to calculating a safety margin between the doses used in animal trials and the estimated human intake, which had been based on a publication by Reagan and Shaw (2007).

The Committee considered that the microbiological analyses should be reported in more detail and should include appropriate controls.

The Committee was concerned that consumers may be misled by the addition of the novel ingredient, which is an animal product, to dairy products that are otherwise regarded as suitable for vegetarians

9. EPA and DHA rich algal oil **ACNFP/101/06**

The Committee was asked to consider this application from Martek Biosciences for the approval of an oil rich in polyunsaturated fatty acids, obtained from the microalga *Schizochytrium sp.*

The Committee was generally content with the data and considered that the toxicological studies were well conducted with appropriate controls and the data were of good quality. The Committee noted that the novel ingredient had potential sustainable and environmental benefits as it was a substitute for fish oils which could help reduce fish catches.

The Committee requested further information on the potential contamination of the product with toxic cyanobacteria. The Committee was also concerned that tests had not been carried out on pregnant and lactating women, a particular target group for high dose supplements containing the novel ingredient .

10. EFSA Guidance on Risk Assessment on Nanoscience and Nanotechnologies to Food and FeedACNFP/101/07

The Committee was asked to consider draft guidance to applicants and risk assessors on carrying out risk assessment of food and feed produced using nanotechnologies. The guidance went out to

consultation on 14 January and the consultation period ends on 25 February. The guidance was also being reviewed by the Food Standards Agency's (FSA) Committee on Toxicology (COT) and advice from both committees would form the basis of the Agency's response to the consultation.

The Committee noted that Table 1 was useful. It noted that there was no evidence that EFSA had examined other international developments, for example in Japan and USA, although this was part of the original mandate. The EFSA guidance did not reflect the European policy of reducing animal testing and asked if EFSA had considered alternatives, for example distinguishing where nano products differ from the non-nanoforms and devising appropriate tests. The Committee also advised that the proposed framework should not be too prescriptive, as it may become rapidly outdated.

The Committee was concerned there was no reference to allergenicity of nanomaterials derived from proteins as there is evidence that the physical form of a protein may affect its digestibility and its allergenic potential.

11. Protein Guidance **ACNFP/101/08**

The Committee is asked to consider the final draft of the document on Protein Guidance.

The Committee agreed the text of the guidance subject to some amendments.

12. Open Meeting Feedback and 2011 workshop. **ACNFP/101/09**

The Committee was asked to consider feedback from the ACNFP open event held in November 2010 and to consider the timing of the next open event. Members were also asked to consider how more of their discussions could be held in open session.

The Committee considered that the next open event should be held in Autumn and that its format and topics for discussion should be discussed further in May.

The Committee sought further advice on the percentage of its meeting which could be opened up as, under the Novel Foods Regulations, there are legal constraints to holding discussions on applications in an open session.

13. Items for Information:

14.1 EU Update **ACNFP/101/10**

14.2 Novel Food notifications **ACNFP/101/11**

14.3 Update on Meat and Milk from Cloned Cattle and their progeny **ACNFP/101/12**

The Committee noted these information papers without comment.

Any other business

The Chair noted that he would shortly be meeting the Agency's Chief Scientist for a routine annual review and asked members to complete a questionnaire by email.

Date of next meeting

The next meeting was scheduled for Thursday 12 May 2011 in Aviation House

(b) Minutes of 102nd meeting (May 2011)

14. Minutes of the 101st meeting **DRAFT/ACNFP/101/Min**

Subject to minor amendments the Committee agreed the minutes were a true record of the 101st meeting of the ACNFP held on Wednesday 9 February 2011

15. Matters Arising and Postal Consultations

Postal paper ACNFP/102/P1: The Committee was consulted by post on an application for authorisation of wheat bran extract and an initial assessment report that was prepared by the Belgian authorities. Members' comments were passed to the European Commission concerning

- labelling (allergy/intolerance and to highlight possible problems with individuals with IBS) and
- biological effect (whether the product, which is intended for use as a prebiotic, would exhibit the same properties as other prebiotics)

The latter point could only be resolved by the provision of additional studies but, as these would be to determine efficacy rather than safety, the UK did not lodge a formal objection. Labelling will be considered when the product comes up for a decision on authorisation.

The Secretariat reported on the following actions following the previous meeting:

Item 5, Dihydrocapsiate: The Committee's opinion was sent to European Commission for review by other MS

Item 7, gamma-Cyclodextrin (CD): Members had commented on additional information that was circulated by post and the FSA wrote to the Commission setting out the Committee's one outstanding concern, which related to the potential for gamma-CD to compromise the intake of fat soluble vitamins (Vitamin D).

Item 8, Phosphated distarch phosphate: FSA had not yet written to EFSA about the difference in views in respect of potential Gastrointestinal effects in children.

Item 11, EFSA guidance on risk assessment of nanomaterials: Comments were submitted to EFSA and have been taken into account in their final revision of the guidelines, which was published on 10 May.

Item 12, Protein guidance: The document was revised and cleared by Members by post. It will be published shortly on the website acnfp.food.gov.uk

16. Taxifolin **ACNFP/102/1**

The Committee considered this application over a number of meetings in 2010 and 2011. The Committee considered the applicant's response to issues raised during the public consultation on this novel ingredient in relation to the presence of saponins, quality control procedures and whether there were appropriate controls in place to monitor for, and control, the presence of mycotoxins.

The Committee was content with the response from the applicant in relation to saponins and quality controls procedures that they employ. The Committee accepted that the quality control procedures for both the raw material and the final product meant that it was unlikely that mycotoxins would be present. A small study carried out by the applicant showed the absence of aflatoxins in the final product and Members were of the view that it would be prudent if the final product was regularly tested to confirm the absence of relevant mycotoxins.

17. Phosphate Distarch Phosphate **ACNFP/102/2**

The Committee had considered this product during 2009 and 2010 and was asked to consider a response from the applicant regarding their outstanding questions about product stability.

The Committee agreed with the applicant's response and thanked the applicant for providing information that was clear and unambiguous and that specifically addressed the Committee's concerns.

18. Rooster Comb Extract **ACNFP/102/3**

The Committee considered this application in February 2011. The Committee was asked to consider the response from the applicant to a number of concerns raised by the Committee at that meeting.

The Committee was content that the novel ingredient was safe. It was concerned that procedures had been carried out properly and therefore sought confirmation that the egg allergic patient sera had been collected with due ethical approval systems in place. The Committee was also content with the applicant's explanation of the calculation of a safety factor based on the "human equivalent dose". It questioned whether the 60kg quoted was the average body weight of a UK citizen. It was informed that 60kg is generally used as the average adult weight in the world population and this provides a degree of conservatism when applied to European populations.

The Committee was content with the microbiological data. The Committee considered that, although the data indicated that intake might exceed the proposed ADI, this was based on a worst case scenario and was unlikely. It considered that there was a need for a better assessment of intake if the novel ingredient is to be used in a wider range of products.

The Committee was concerned that the labeling would not be specific enough for vegetarians, noting that vegetarian diets are more common in the UK than in some other member states.

Consumers would not expect to see animal products in milk products and products should carry a prominent statement such as "not suitable for vegetarians".

The Committee was concerned that the health claims for healthy joints may be misleading as there was no evidence that this ingredient would lead to this outcome.

The Committee noted that a number of respondents to the consultation on this dossier had been concerned about animal welfare issues. The Committee asked for confirmation that the combs were removed from chickens which had been raised and slaughtered for human consumption. If so, it could be satisfied that the procedures for obtaining the combs would not affect the welfare of the birds adversely.

19. EPA and DHA rich oil from algae (*Schizochyrium sp*) **ACNFP102/4**

The Committee first considered this application in February 2011. The Committee was asked to consider the applicant's response to concerns raised by the Committee at that meeting in relation to high dose supplements that were targeted at pregnant women and nursing mothers, and to potential microbiological contamination during fermentation.

The Committee noted the potential benefit of this type of product for maintaining adequate intakes of long chain omega-3 fatty acids, as an alternative to fish oils.

The Committee considered however that the applicant had not fully addressed its concerns in relation to the consumption of high doses of DHA and EPA by pregnant women and nursing mothers. In particular the Committee requested that the applicant consider studies which link intake of fish oil to increased gestation periods.

Members were partially reassured by the applicant's response in regard to *Cyanobacteria* but asked for confirmation whether light was excluded from the fermentation process. Members also advised that testing for *Cyanobacteria* should be included in the quality control strategy.

20. Chia Seed (Additional use) **ACNFP/102/5**

The Committee was asked to consider an application from The Chia Company, to extend the use of their chia seeds in foods other than bread.

The Committee accepted that chia seeds would only be incorporated into products where seeds were commonly usually found, namely breakfast cereals (e.g. muesli), biscuits and other baked products and fruit, nut and seed mixtures (sprinkles).

The Committee recognized that individuals with seed allergies may not always avoid these products but did not think there was a substantial risk from extending the use of chia seeds, particularly if this was accompanied by communication with "at risk" groups. The Committee therefore considered that the applicant should fulfill its positive commitment to contact patient groups.

The Committee noted that the applicant's intake estimates did not include children and also recalled the discussion on under-reporting in food consumption surveys from the previous meeting. The Committee stressed that a positive opinion on the extension of use would not imply endorsement of any health benefits attributed to consumption of the seeds.

21. Novel Sources of Selenium and Zinc. **ACNFP/102/06**

The committee was asked to note that zinc L-pidolate has previously been cleared by EFSA as a source of zinc and that selenitetriglycerides will be evaluated in due course by EFSA as a source of selenium.

As new sources of vitamins and minerals undergo parallel authorisation procedures under sector-specific legislation and under the novel foods regulation, they are inevitably evaluated by EFSA before an authorisation can be granted in the EU. To avoid duplication of effort, national authorities for novel foods usually rely on the centralised assessment that is carried out under the other legislation, so that novel food authorisation is based on an EFSA opinion rather than a detailed opinion from one or other member state. In this case, the Polish competent authority for novel foods had carried out a national assessment and the Committee was invited to highlight any specific concerns they would like to bring to EFSA's attention about selenitetriglycerides, in the light of the Polish report. The Committee highlighted the need to assess the bioavailability of this new source of selenium and whether this formulation with triglycerides altered its distribution and accumulation within the body, for example in adipose tissue. These questions had not apparently been considered by the Polish assessors.

The Secretariat agreed to pass these comments on to EFSA as part of the UK's response to the initial opinion.

22. Recent notifications **ACNFP/102/07**

The Committee was asked to consider two recent opinions from other EU Member States on (substantial) equivalence where the basis for the comparison was a similar product obtained from another species, and whether, in the light of these opinions, it wished to review its guidance on the submission of requests for opinions on equivalence in the UK. One of the opinions was a comparison between squid oil and tuna oil, the other a comparison between sugar cane fibre and bamboo fibre.

The Committee considered that in both cases the taxonomic differences were too great to allow a meaningful comparison. The Committee did not see any need to update its existing guidelines, which state that the novel and existing products should be derived from closely related species in order to demonstrate substantial equivalence. The Secretariat noted that this issue was expected to be discussed at EU level over the coming months and that this may necessitate a future review.

23. EU novel foods regulation **ACNFP/102/08**

The Committee was asked to note the outcome of EU negotiations on the proposals to update the EU novel foods regulation.

The Committee noted the EU's legislative bodies had been unable to reach agreement on updating the EU novel foods regulation and considered that a new proposal would stand more chance of success if the issues related to animal cloning are treated separately.

24. ACNFP Advice **ACNFP/102/09**

The Committee was asked to consider a table setting out the Committee's advice for a number of novel food applications between 2008 and 2010, alongside the eventual outcome of the applications. The table had been developed in response to a request by members for an overview of how the Committee's recent advice has been implemented.

The Committee noted that the Secretariat intended to update this information annually and commented that it was a useful paper. The Secretariat confirmed that the paper would be put on the Committee's website and could be referred to in future open events.

The Committee asked why, on occasions, the UK abstained rather than voting against a proposal. The Secretariat explained that as the decisions were taken by qualified majority the net effect of abstaining was the same as voting against, as it was the strength of the favourable vote which was important. A vote against authorisation might be appropriate where there was evidence that a novel ingredient presented a risk to consumers, while abstaining would be appropriate where there was insufficient proof of safety.

The Committee also noted the number of pending decisions and asked whether applications were ever withdrawn and whether ACNFP advice was reflected in the final authorisation decisions. The Secretariat explained that there were various reasons why applications remained pending, for example complex risk management decisions or awaiting additional information from an applicant. The Secretariat agreed to look at ways to incorporate additional information into the table, and possibly including ACNFP advice from previous years.

The Committee noted that withdrawn products would be included in future versions of the table.

25. Items for Information:

13.1 EU Update **ACNFP/102/10**

The Committee noted this information paper without comment.

13.2 Update on Scientific Advisory Committees (SACs) **ACNFP/102/11**

The Chairman reported on the General Advisory Committee on Science (GACS) meeting which took place in early March, when he had given a presentation on the work of the ACNFP.

26. Any other business

The Chairman reflected on his appraisal discussion with the FSA's Chief Scientist, Dr Andrew Wadge. The Chairman reported that Dr Wadge had encouraged the Committee to discuss generic issues in its meetings as well as routine applications for novel foods.

The Chairman fed back comments made by ACNFP Members via their appraisal questionnaires. Two common themes had emerged: Members asked that papers be sent out at least 10 days before each meeting, and they praised the excellent support provided by the Secretariat.

27. Date of next meeting

The next meeting was scheduled for Thursday 7 July 2011 in Aviation House

(c) Minutes of 103rd meeting (September2011)

28. Minutes of the 102nd meeting **DRAFT/ACNFP/102/Min**

The Committee agreed, by a postal consultation in July, the minutes were a true record of the 102nd meeting of the ACNFP held on Thursday 12 May 2011.

29. Matters Arising and Postal Consultations

Due to a relative lack of substantive discussion items, the Committee meeting scheduled for July had been cancelled and Members were invited to consider the following papers by post.

Rooster Combs Extract	**ACNFP/103/P1**
Chia seed (additional use)	**ACNFP/103/P2**
Open Event	**ACNFP/103/P3**

In addition, the FSA subsequently received four documents from the European Commission and from EFSA that required the Committee's consideration in advance of this meeting:

EFSA Draft Guidance on Repeated-Dose 90-Day Oral Toxicity Studies on Whole Food/Feed in Rodents	**ACNFP/103/P4**
GABA-enriched *Lactobacillus* ferment	**ACNFP/103/P5**
Arachidonic acid-rich fungal oil	**ACNFP/103/P6**
DHA and EPA rich microalgal oil	**ACNFP/103/P7**

The Open Event is discussed under item 10 below. The Secretariat summarized the outcome of the other postal consultations in a tabled paper, which is attached as an annex to these minutes. Members agreed that the Committee's final opinion on rooster combs extract should include a statement about the apparent lack of evidence for any health benefits for this product. This opinion would be forwarded to the Commission as the basis of a favourable assessment report from the FSA, as the UK competent authority for novel foods.

30. Polyvinyl Methyl Ether Maleic Anhydride Co-Polymer

(Synthetic Chewing Gum Base) **ACNFP/103/1**

The Committee was asked to consider the Dutch Competent Authority's initial opinion on this application for authorization of this synthetic chewing gum base.

The Committee agreed with the favorable opinion of the Dutch whilst noting the following comments.

The Committee was satisfied with the toxicology data, and it had no concerns about nutrition or allergenicity. The Committee noted that the applicant had provided research studies which demonstrated that synthetic chewing gum base or derivatives have inhibitory effects on oral bacteria and therefore questioned whether the novel ingredient might also have effects on human gut microflora . In the absence of human studies to investigate this, the Committee asked if the applicant had any further information on this issue. . The Committee also supported the Dutch request that the applicant provides comprehensive data relating to levels of contaminants as part of the specifications of the novel ingredient and emphasized the importance that robust methods are supplied in the dossier to determine levels of contaminants. The Committee was also concerned there was insufficient clarity about what remained of the polymer when the novel ingredient was produced.

The Committee considered that adults over 50 were not typical consumers of this novel ingredient, and children consumed significantly more gum than adults. At the levels consumed the Committee did not consider the intake of the novel ingredient presented a safety concern.

31. Extension of the Uses of Antarctic Krill Oil **ACNFP/103/2**

The Committee was asked to consider the Finnish Competent Authority's initial opinion on this application for the extension of uses of krill oil, bringing them into line with those of other oils that are authorised under the novel foods regulation as sources of docosehexaenoic acid (DHA).

Although the Committee was not concerned about the intake of krill oil and DHA for this application in isolation, it did express concern about cumulative exposure from the increasingly wide range of dietary sources of DHA, which it had previously identified as having potential implications for vulnerable groups such as pregnant women.

The Committee noted that intake of contaminants is the limiting factor for the consumption of oily fish and asked the Secretariat to investigate the levels of contaminants such as heavy metals and dioxins in krill oil.

The Committee noted that the oil will be labeled to indicate that it is derived from a type of crustacean, in line with allergen labelling requirements. However, the widespread use of the oil could lead to a restriction of choice for people with an allergy to crustaceans. The Committee re-iterated that, being derived from an animal source, the oil would not be suitable for vegetarians.

32. Gamma Cyclodextrin **ACNFP/103/3**

The Committee considered the Irish Competent Authority's initial opinion following a postal consultation in September 2010 and reviewed additional information at its meeting in February 2011. The Committee was asked to consider the response from the applicant to the concern raised at the February meeting that gamma-cyclodextrin might interfere with the absorption of fat-soluble vitamins, particularly vitamin D.

At that meeting the Committee had advised that the applicant should carry out a human study to validate the suggestion that the presence of gamma-cyclodextrin the diet would not compromise the uptake of fat soluble vitamins. The applicant's response to this request argued that a human study was not appropriate and suggested an alternative animal study.

The Committee did not accept the view of the applicant that the human study was not appropriate, but noted that an *in vitro* study with cyclodextrins showed differences in stability between complexes formed with beta and gamma cyclodextrin. The Secretariat agreed to seek additional information from the applicant.

33. Licorice Root Extract **ACNFP103/4**

The Committee was asked to consider a favorable European Food Safety Authority (EFSA) opinion on this licorice root extract, and whether it answered the concerns that the Committee had raised when it considered this novel ingredient in April 2009.

The Committee was satisfied with information on the composition of the extract and on haematological effects. However, the intake levels by children had not been addressed and the Committee was concerned that the applicant's proposal to label products as not suitable for children would not prevent them being consumed by younger age groups, particularly as the ingredient was proposed for use in foods such as yoghurt and fruit drinks that are likely to be attractive to children.

The Committee maintained its view that novel ingredient was not well specified. In particular the residual polyphenol content of 20% was calculated by difference rather than by analysis.

The Committee accepted that the novel ingredient would be unlikely to be consumed by children if use was restricted to food supplements, and agreed that there was adequate reassurance of safety if the daily intake did not exceed the 120mg/day level viewed to be safe by EFSA.

34. ACNFP advice **ACNFP/103/5**

The Committee was asked to consider a revised table detailing its advice on recent novel food applications and the current status of the relevant dossiers.

The Committee thanked the Secretary for the paper and commented that it was a useful and interesting paper which should be updated on an annual basis.

35. EFSA Draft guidance on the risk assessment of food and feed derived from GM animals. ACNFP/103/06

The committee considered an EFSA consultation on draft guidance for the risk assessment of products derived from GM animals. The guidance is intended to cover all food producing animals and fish, as well as crustaceans and molluscs. Insects and other invertebrates have not been taken into account, with the exception of honey bees that are used in agricultural practice.

Comments from the Committee were to be collated and submitted online to the consultation website by the deadline of 30 September. The Committee highlighted that the document appeared to be an adaptation of the existing requirements for GM plants when a fresh approach would probably be more beneficial, concentrating on the measurement of the functional outcomes of the genetic modification. The Committee also identified several deficiencies in the guidance that needed to be addressed, as well as questioning a number of specific points in the guidance.

36. Open Event

The Committee had agreed the format of the Open Event and suggested two topics for discussion (nanotechnology and animal cloning) following a postal consultation in July. The Committee was asked to consider the agenda for the Open Event and to further consider the topics for the discussion in small breakout groups.

The Committee agreed the agenda which had been drawn up by the Secretariat following the postal consultation, subject to some amendments. It had no further suggestions for topics for discussion.

37. Items for Information:

11.1 Maternal and foetal exposure to pesticides associated with GM foods **ACNFP/103/08**

11.2 EU Update **ACNFP/103/09**

11.3 Update on Scientific Advisory Committees (SACs) **ACNFP/103/10**

11.4 Independent Review of SACS **ACNFP/103/11**

The Committee noted these information papers without comment.

Any other business

Peter Shewry reported on a recent meeting of the Chairs of government committees, hosted by the Government Chief Scientific Adviser, which he had attended on behalf of the ACNFP Chair. The Committee agreed this was a useful forum for exchange of best practice and it was also of value to see the range of Committee work across Government.

Jayam Dalal reported on a recent meeting she had arranged where a group of ACNFP members and a member of the FSA's Novel Foods Unit met representatives of the Hindu Community in Wembley. All those who attended agreed the discussions on animal cloning and betel nut were very useful. The Committee members who attended this meeting considered it had helped them to have a greater understanding of the Indian community and had provided a bridge between consumers and technical experts (including expert ACNFP members) which would help people to make safe choices about food.

Date of next meeting: Thursday 24 November 2011 in Aviation House, to be followed by the Open Event.

Annex to ACNFP/103/Min

Outcome of Postal Consultations

Rooster Combs Extract **ACNFP/103/P1**

The draft opinion attached to the paper was agreed, after minor amendments, and

was published on the ACNFP website on 28 July for 10 day public consultation. Fifteen public comments were received. None was substantive in terms of raising additional safety considerations, but the comments repeatedly raised issues relating to animal welfare, suitable labelling for vegetarians, and general disapproval of the concept of using such an ingredient.

Members reviewed the public comments by email and the draft opinion has been revised to take into account a number of proposed amendments.

Before seeking clearance of the final text from the Chairman, the Secretariat noted that several Members also raised concerns about the apparent lack of evidence for any health benefits for this product. Similar questions have been raised previously in respect of other novel food applications. The Secretariat has therefore drafted some standard text that might be used to cover this point in future opinions, along with a sentence to reflect their views on the current application (attached). If Members are content with this text, it will be included in the present opinion.

Chia seed (additional use) **ACNFP/103/P2**

Members were asked to consider the text of the draft opinion that reflected their discussions on this application for additional use of chia seeds as a novel food ingredient, taking into account points that had been raised by members of the public.

Specific questions about potential allergy to chia seed are to be resolved by the relevant Members who are expert in this field and the Secretariat will discuss this with them in the near future.

Once these questions are agreed, the draft opinion will be published via the Agency's web-site for the usual 10-day public consultation. After the Committee has considered any public comments and its opinion is finalised, the final opinion will be forwarded to the Commission.

EFSA Draft Guidance on Repeated-Dose 90-Day Oral Toxicity Studies on Whole Food/Feed in Rodents **ACNFP/103/P4**

Members were invited to comment on this draft guidance, which was the subject of a public consultation by EFSA.

The following comments from Committee Members were submitted to EFSA by the deadline of 18 August. (Comment 4, attributed to the FSA, is the result of comments received from UK toxicologists by the FSA's Chemical Risk Assessment Unit.

Comment 1

The guidance is built on advice for the assessment of GMOs where the aim is to ensure that "the GM food is as safe and nutritious as its traditional counterpart". In such cases, the "obvious" comparator is the isogenic comparator (without the genetic modification).

With whole foods, there is no obvious comparator and EFSA have attempted to address this by advising that "diets should be adjusted if the levels of nutritionally important ingredients differ by more than 5% between different test groups. With this in mind, purified diets are often preferred as the use of refined ingredients" Superficially this looks like a reasonable approach to take but it ignores the following points:

1. Issues of physiochemical properties of diets which are likely to differ between whole foods and purified diets which aim to reflect their chemical composition. For example, a whole food could contain exactly the same amount of starch as the purified diet control but evoke very different intestinal, endocrine and other effects if the starch in the whole food was relatively unavailable for digestion by pancreatic enzymes because of its cellular nature.

2. Many components of whole foods could have nutritional effects. Does the EFSA committee intend that such "balancing" between the control and test diets should be restricted to macronutrients or apply to all nutrients? What about individual

fatty acids or amino acids or other non-nutrient bioactive ingredients e.g. isoflavones?

I don't have an easy answer to these questions but I think that:

a) This complexity should be acknowledged in the Guidance;

b) Investigators should be encouraged to address these issues on a case-by-case basis. In other words, when designing their studies, they should be advised to consider what features/ characteristics of their whole food might affect outcomes and to be explicit in stating how they have addressed the design of their Control diet(s).

Comment 2

Overall this is a useful document and addresses the topic from a practical perspective including all of the normal OECD GLP and guideline principles.

The statistical aspects of the topic have been addressed fully and completely which one would hope would be helpful to anyone contemplating conducting a study. Equally the observations to be carried out are given in sufficient detail, but on occasions recommendations are not justified (e.g. 45-day blood samples). I cannot quite see the rationale for including more endocrine endpoints for these types of study however widely they are being promoted for REACH-type studies since the objectives are rather different.

Comment 3

If I were setting out to design a study, the guidance that is missing here is on the choice of comparator or control for the test product. This choice is critical to the success of any such study and a poor choice would make all the statistical power considerations rather pointless. I would have expected some more detailed discussion on this point, while recognising that it is very much a case-by-case consideration. For GM products this aspect has been given some consideration in other guidance, but I am not aware of anything similar for novel foods. The concept of nutritional equivalence is addressed but this is probably not so important since the dose levels are recommended to avoid nutritional imbalances. I would particularly consider that there is a need for some recommendation that the control group should receive a nutritionally comparable and toxicologically characterised material. The aim being to avoid the use of control material which, although widely consumed is not toxicologically sufficiently characterised to allow interpretation of experimental findings.

Comment 4 (FSA)

Overall UK toxicologists have welcomed the guidance as providing useful advice when carrying out 90 day feeding studies on whole foods. However, there is some concern about creating a situation where applicants have to comply with two different sets of guidelines (EFSA and OECD) which may result in duplication of experiments and an increase in the number of experimental animals used and this situation should be avoided at all cost. Therefore, the guidance should make it clear in the introduction its status in relation to the OECD guidelines.

GABA-enriched *Lactobacillus* ferment **ACNFP/103/P5**

Members were asked to consider an initial opinion from the Irish authorities on this novel ingredient, which concluded that an additional assessment was required due to the lack of toxicological data.

Members agreed with the Irish conclusions, highlighting the need for the product to be fully characterised and for data to be provided on the safety of the complete product, rather than its supposed constituents. Members also highlighted specific aspects of the potential toxicity of gamma-amino butyric acid (GABA) and questioned the applicant's rationale for advising selected "at risk" groups not to consume the product.

The Food Standards Agency has transmitted these comments to the European Commission so that they can be addressed in any additional assessment of this product.

Arachidonic acid-rich fungal oil **ACNFP/103/P6**

Members were invited to comment on an initial opinion from the Dutch authorities on an application for the use of a new source of arachidonic acid, for addition to infant formula.

Members were satisfied with the thoroughness of the Dutch assessment and the Food Standards Agency, as the UK competent authority for novel foods, therefore confirmed to the Commission that they had no comments or objections to the use of this new ingredient. Members had a number of

comments relating to the use of arachidonic acid in infant formula however, as the use of the acid is already permitted, then this was viewed to be a generic issue.

DHA and EPA rich microalgal oil **ACNFP/103/P7**

Members were invited to consider further information provided by the applicant concerning microbiological controls on the manufacture of this novel ingredient, and on the effect of high level intake of DHA (docosahexaenoic aicd) and EPA (eicosapentaenoic acid) increasing gestation times. Members were also asked to review a draft opinion that reflected their earlier discussions on this application.

Members were satisfied with the additional information regarding microbiological controls, but did not regard the issue of increased gestation times to have been adequately addressed by the applicant. Although not specific to this source of DHA and EPA, Members requested that this issue is reflected in the opinion.

The revised opinion will now be cleared by Chairman's action and issued for the usual 10-day public consultation.

ACNFP OPINION ON ROOSTER COMB EXTRACT

Standard text applicable to most novel food applications:

> The Committee's assessment focuses on safety and labelling and does not address any nutrition or health benefits that may be claimed for the novel ingredient or for foods that containing it. Nutrition or health claims may only be made if they are specifically authorised under EU Regulation (EC) No 1924/2006.

Specific text for this product:

> In the case of Rooster Comb Extract, which is proposed as a dietary source of hyaluronic acid, the Committee notes that this substance is produced endogenously in the human body, and that EFSA has advised that a cause and effect relationship has not been established between the consumption of hyaluronic acid and the maintenance of normal joints [reference].

reference:
EFSA Journal 2009; 7(9):1266 http://www.efsa.europa.eu/fr/efsajournal/pub/1266.htm

(d) Minutes of 104th meeting (Nov 2011)

38. Minutes of the 103rd meeting **DRAFT/ACNFP/103/Min**

The Committee agreed the minutes were a true record of the 103rd meeting of the ACNFP held on Wednesday 21 September 2011

3. Matters Arising and Postal Consultations

The Secretariat reported on the actions following the previous meeting:

Item 3.1 Rooster Combs Extract: The UK opinion was submitted to the Commission on 9 November.

Item 3.2 Chia seed (additional use): The Secretariat would organise a teleconference with Members who had outstanding concerns on the text of the draft opinion, relating to the allergenic potential of chia seed.

Item 4 Polyvinyl Methyl Ether Maleic Anhydride Co-Polymer (Synthetic Chewing Gum Base): UK sent objections to the Commission on 13 October, referring to the need for assurance that the NI does not have effects on gut microflora.

Item 5 Extension of the Uses of Antarctic Krill Oil: the FSA sent comments to Commission on 17 November agreeing that this novel ingredient should be approved. The letter noted that the ACNFP had asked about the implications of consuming a range of marine oil products in relation to overall intakes of contaminants. Given that EU legislation already specifies maximum contaminant limits for marine oils and other relevant foods, the Agency felt that this afforded sufficient protection to consumers.

Item 6 Gamma Cyclodextrin: Secretariat has received a response from the applicant and comments from an ACNFP member, and is discussing these with the SACN Secretariat.

Item 7 Licorice Root Extract: A decision in favour of the marketing of the extract was approved by majority vote at a Standing Committee meeting on 13 October.

Item 9 EFSA draft guidance on the risk assessment of food and feed derived from GM animals: Comments from Committee Members were submitted to European Food Safety Authority (EFSA) by the deadline of 30 September.

4. DHA and EPA Rich Microalgal Oil **ACNFP/104/1**

The Committee was asked to consider public comments received following the publication of the draft initial opinion on this application for authorisation of a Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) rich oil from the microalgae *Schizichytrium.* The Committee previously considered this application at its meetings in February and September 2011.

The Committee reviewed comments received during the public consultation and agreed minor amendments to the opinion in relation to increased gestation. The opinion would form the basis of the UK initial opinion for this product and would be forwarded to the European Commission. The Committee also noted EFSA was undertaking a review into the safety of long chain fatty acids and is likely to report in March 2012.

5. DHA Rich Oil from the Microalgae *Schizochytrium sp.* **ACNFP/104/2**

The Committee was asked to consider a new request for an opinion on substantial equivalence of this novel food ingredient compared with, its existing counterpart, an oil extracted from a different strain of the same genus.

The Committee questioned the taxonomic classification of the source organism and also requested more information about variability in the composition of the product and the methods of analysis. It would then be possible to determine whether the novel ingredient was substantially equivalent.

6. Coriander Seed Oil **ACNFP/104/3**

The Committee considered the Irish Competent Authority's initial opinion on an application for coriander seed oil to be incorporated into food supplements.

The Committee noted that coriander seed powder was used widely as a spice by particular populations. Characteristic components of the oil, such as petroselenic acid, were also found in parsley and other umbelliferae plants. However, the Committee noted that consumption of the oil in food supplements would be twenty times higher than the current average consumption from the spice. The Committee sought further information on the metabolism of the petroselenic acid and impact on the metabolism of other fatty acids at these intended doses.

The Committee noted that there could be up to 100mg of protein in 100g of coriander seed oil, and a 600mg dose could contain 0.6 mg of protein which is sufficient to cause a severe allergic reaction. The Committee observed that protein levels had been analysed using the Kjeldahl method, which had been rejected by the European Food Safety Authority (EFSA) when evaluating products for

potential exemption under allergen labelling rules. The Committee was therefore concerned there was insufficient evidence to support the applicant's suggestion there would be no allergic reaction to the novel ingredient, particularly as coriander is botanically related to celery, which is a significant food allergen.

For these reasons, The Committee stated did not agree with the positive conclusions in the Irish opinion.

7. Synthetic Vitamin K_2 **ACNFP104/4**

The Committee was asked to consider the application dossier on this novel food ingredient and to give preliminary comments in advance of the German competent authority's initial opinion being circulated to Member States.

The Committee indicated that the data provided in the dossier was of good quality and did not appear to give cause for concern in regard to allergenicity and toxicity.

The Committee noted that Vitamin K deficiency was an increasing problem and the existing safety evaluation of Vitamin K2 could be strengthened by the data in this application.

8. Micro RNAs **ACNFP/104/5**

The Committee was asked to consider a recently published article that reported the discovery of stable plant microRNAs in mammalian (including human) serum and plasma. This suggested that these miRNAs are capable of surviving passage through the mammalian gut and being absorbed through the gut wall into the bloodstream. The most abundant of these miRNAs, which is present at high levels in rice, was also shown to influence mammalian gene expression.

The Committee found this paper extremely interesting in terms of the interaction between the food constituents of plants and their influence on the human body, while emphasizing that this was an entirely natural phenomenon and that people have always consumed these RNA molecules as part of their diet. Members agreed that a number of the findings were unexpected and these findings needed to be confirmed by other research groups.

In terms of the risk assessment of GM foods, miRNAs produced by GM plants would be no different from those produced ordinarily by non-GM plants, but researchers need to be aware of the results of this work and follow up studies need to be monitored to assess their implications. There are currently no applications for authorization of GMOs expressing miRNAs, but current GM risk assessment guidelines should be adequate to cover any future application of this technology in the production of GM plants.

The Committee was informed that the paper was due to be discussed at a meeting of the Advisory Committee on Releases to the Environment in early December.

9. Open Workshop

The Committee was updated on arrangements for the Open Workshop which was to take place after the Committee's meeting. It agreed the questions for the breakout groups and noted the final arrangements for the workshop.

10. Items for Information:

10.1 Alternative Protein Sources **ACNFP/104/6**

10.2 EU Update **ACNFP/104/7**

10.3 Update on Scientific Advisory Committees (SACs) **ACNFP/104/8**

The Committee noted these information papers without comment.

11. Any other business

The following items were discussed:

11.1 Consumer Advisory Panel: The Consumer Representatives on the Committee reported that the FSA had recently set up a new Consumer Advisory Panel. Panel membership consists of consumer representatives of the FSA's Advisory Committees. Membership will run in parallel with appointment to a committee. The ACNFP was represented on the panel by Christopher Ritson, Jayam Dalal and Gillian Pope. The Chair would be jointly held by a senior FSA manager and a member of the panel.

ACNFP members on the panel considered it would be useful to bring issues from the scientific committees to the panel. The next meeting of the Consumer Advisory Panel was scheduled for February 2012.

11.2 ACNFP Review: The Committee was updated on the independent review that was currently being undertaken on behalf of the FSA. A report would be presented to the Committee in due course, once the review was completed.

11.3 General Advisory Committee on Science (GACS): The Chair of the Committee reported on the GACS meeting held on 9 November, which included a useful presentation of the work of the Advisory Committee on Microbiological Safety of Food. As a result of discussions at various meetings, the secretariats for SACN, ACNFP and COT together with officials from DH were meeting to discuss intake levels resulting from multiple foods containing similar ingredients.

12. Date of next meeting

The next meeting was scheduled for Wednesday 15 February 2012 in Aviation House.

COMMITTEE ADVICE ISSUED DURING 2011

(a) OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR SYNTHETIC DIHYDROCAPSIATE

Applicant: **Ajinomoto Co. Inc.**

Responsible Person: **Andrew Cockburn**

EC Classification: **1.2**

Introduction

1. An application was submitted to the Food Standards Agency in August 2010 by Ajinomoto Co. Inc for the authorisation of synthetic dihydrocapsiate (DHC) as a novel ingredient in the EU. A copy of the application was placed on the Agency's website for public consultation.

2. Dihydrocapsiate was first discovered in CH-19 Sweet (a non-pungent variety of chilli pepper) along with capsiate. Sourcing of large quantities of dihydrocapsiate from chilli peppers is not sustainable because of the relatively small amounts that are contained in and can be extracted from chilli peppers.

3. Both dihydrocapsiate and capsiate occur naturally in edible pungent (hot) and non-pungent chilli peppers. They are analogues of capsaicin, the pungent component of chilli peppers, but unlike capsaicin they do not create the sensation of "hotness". Dihydrocapsiate and capsiate have an ester bond in place of the amide bond of capsaicin between the vanillyl and fatty acid moieties.

4. The applicant mentions in the dossier that capsinoids are able to enhance energy expenditure and fat oxidation.

5. The applicant reports that an extract of capsinoids from CH-19 Sweet chilli pepper is marketed as a food supplement in the EU (Czech Republic and France) and in the US and Japan.

6. The applicant intends that synthetic dihydrocapsiate (DHC) will be incorporated into a range of foods such as baked goods, beverages, confectionery, cereals and desserts and other foods including ready-to eat frozen meals, soup, sweeteners and salad dressings.

7. DHC has been classified as a pure chemical or simple mixture from non-GM sources where the source of the novel food has no history of food use in the EU (class 1.2 accoridng to the scheme in Commission Recommendation 97/618 (EC)).

I. Specification of the novel food

Information on this aspect is provided on p. 10-15 of the application dossier

8. The chemical and physical specification for DHC has been established by the applicant and can be found in the table below.

Test Item	Test Method	Acceptance Criteria
Description	JSFA V11, general notices	Viscous, colourless to yellow liquid
Identification (IR)	FCC V, Infrared Spectra	It exhibits absorption at the wave number of around 2953, 2928, 2855, 1733, 1519, 1278, 1241, 1036, 818 and 798 cm^{-1}
Specific Gravity	FCC V, Specific Gravity	1.02 to 1.03
Starting Materials	HPLC	Vanillyl alcohol: not more than 1.0% MNA*2% to 7%
Related Substances	HPLC	Not more than 2%
Residual Solvent (n-hexane)	GC	Not more than 5 mg/kg
Assay (DHC)	HPLC	≥ 94 %
Magnesium	JSFA VII, Atomic Absorption Spectrophotometry	Not more than 1 mg/kg
Copper	JSFA V11, Atomic Absorption Spectrophotometry	Not more than 1 mg/kg
Arsenic	JP XIV, Arsenic Limit Test, Method 4	Not more than 1 mg/kg
Cadmium	FCC V, Flame Atomic Absorption	Not more than 1

	Spectrophotometric Method	mg/kg
Lead	FCC V, Lead Limit Test, Flame Atomic Absorption Spectrophotometry	Not more than 1 mg/kg

FCC V: Food Chemicals Codex Fifth Edition

JSFA VII: The Japan's Specifications and Standards for Food Additives Seventh Edition.

JP XIV: The Japanese Pharmacopoeia Fourteenth Edition

GC: Gas Chromatography

HPLC: High-Performance Liquid Chromatography

*MNA = 8-methylnonanoic acid

9. The applicant has provided results of analysis of seven independently manufactured lots of commercial grade DHC produced on a pilot scale over a three month period which demonstrates that all lots conformed with the set specifications. The applicant states that it was demonstrated over this period that the manufacturing process and final product are highly reproducible and that the process is capable of consistently producing material that meets the above specifications. The analysed batches were produced on a pilot scale but using the same type of industrial equipment so the applicant states it is therefore reasonable to expect that scaling up of the process will not result in changes to the composition of DHC preparations.

10. The product contains a minimum of 94% DHC and the impurities have also been characterised. Analyses of the same seven batches revealed the presence of reaction products or related substances which comprised between 0.69 and 1.39% of the product. The applicant has identified four major by-products which accounted for 77 to 91% of total other related substances, namely vanillyl 6-bromohexanoate, vanillyl decanoate, vanillyl dihydrocapsiate and a diacyl ester. Of these, vanillyl dihydrocapsiate was the largest individual impurity with a concentration of 0.73%.

11. Residues of the extraction solvent n-hexane are kept to specifications (less than 5 parts per million).

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

Information on this aspect is provided on p 16-20 of the application dossier

12. DHC is produced by esterification of vanillyl alcohol (V-OH) and 8-methylnonanoic acid (MNA) using an immobilised food grade lipase preparation. The lipase enzyme is produced by Novozymes Denmark (Novozyme®435 FG, declared activity 1000PLU/g) and according to the applicant is approved in the EU as a processing aid (approval reference number 2006-20-5406-00106).

13. After esterification, the reaction is quenched with the addition of n-hexane. The lipase and V-OH are removed by filtration steps.

14. The applicant has presented details of stability studies which show that DHC is stable for at least 2 years at either 5°C or 20°C. The applicant has determined the shelf-life of the product to be 12 months (minimum).

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

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

Information on this aspect is provided on p 36-42 of the application dossier

15. The applicant plans to produce DHC for use by third party food manufacturers but will not itself manufacture foods containing DHC. The applicant intends that DHC will be incorporated into a range of foods such as baked goods, beverages, confectionery, cereals and desserts and other foods including ready-to eat frozen meals, soup, sweeteners and salad dressings. Therefore, the applicant is seeking approval for use of DHC in these foods at levels that will deliver 3 mg per portion or serving. The proposed use levels have been calculated so that each portion of a given food product will contain 3 mg of DHC. The actual DHC concentration in any food will therefore depend on that manufacturer's product specification for single serve products or on the typical or recommended portion sizes for products presented in multi-serve packs.

16. Individual intake of DHC will depend on how many servings of food containing 3 mg of DHC are consumed. The applicant has provided a detailed section on potential intakes in the dossier. The applicant anticipates that DHC-containing foods will normally be consumed by adults, but has calculated intakes for all potential consumers.

17. The applicant estimates that, based on UK and European food consumption patterns, average adult intakes are not likely to exceed 25 mg/day (0.4 mg/kg bw/day) and high level intakes are not likely to exceed 40 mg/day (0.7 mg/kg bw/day). These estimates are based on the conservative assumption that all possible foods in an individual's diet contain 3mg DHC per portion. The applicant further states that if children were to consume DHC in all foods which could potentially contain it, their average intake could be up to 15 mg/day (1 mg/kg bw/day) and high level intake may approach 30 mg/day (2 mg/kg bw/day). The applicant indicates that

dihydrocapsiate from natural sources is unlikely to contribute significantly to European intakes so these sources have not been included in these calculations.

***Discussion**: The Committee raised a question relating to intake estimation in view of the broad range of products to which DHC is intended to be added. Exposure specialists in the Food Standards Agency advised that the applicant's approach using NDNS data and the EFSA concise database was reasonable, particularly as the modelling was done on a wide range of food groups. Therefore, no further information was requested from the applicant on this issue. Setting levels on the basis of portion sizes has been used in previous novel food applications where an applicant has provided information about the use level required to achieve a particular level of intake, based on typical portion sizes. The Committee did not raise any further questions relating to this issue.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p 43 of the application dossier

18. The applicant states that synthetic DHC is identical to dihydrocapsiate found naturally in peppers and can therefore be considered to be nutritionally equivalent to the natural product and likewise has negligible nutritional value.

***Discussion**: The Committee sought clarification of the purpose of adding DHC to foods. The applicant highlighted that chillies can have desirable properties for consumers e.g. providing a feeling of refreshment or well being. The addition of DHC is intended to provide the same response but without the strong hot taste. The Committee remained sceptical about the purpose of incorporating DHC into foods but this was not a safety-related concern.*

XII. Microbiological information on the novel food

Information on this aspect is provided on p.15 and p44 of the application dossier

19. The applicant has provided microbiological data from 4 independent lots of DHC, where total aerobic counts were <3000 CFU/g, yeast and mould counts were <100 CFU/g and all lots were negative for Coliforms.

***Discussion**: The Committee did not raise any concerns or questions on this aspect of the application.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 45-75 of the application dossier

Metabolic fate of DHC

20. The applicant states that, based on toxicokinetics data in rats, the highest concentrations of DHC after oral dosage are found in the major organs or systems of absorption, metabolism and excretion (the GI tract, liver and kidney). DHC is metabolised by hydrolysis in the gut and the metabolites are rapidly absorbed and conjugated in the liver and eliminated predominantly by the kidneys into the urine. The applicant concludes that accumulation of DHC or its metabolites in the tissues is unlikely to occur due to its rapid absorption, short half-life and high level of excretion.

21. The applicant has also summarised relevant studies on the metabolic fate of CH-19 Sweet extract (which contains ca. 7.5% capsinoids, around 20% of which is dihydrocapsiate). These studies showed that capsinoids from CH-19 sweet extract are metabolised in the GI tract and or gut mucosa (or both) before absorption. The absorbed vanillyl alcohol found in the portal vein undergoes metabolic conversion by sulphation and glucuronidation during its passage through the liver before entering into the post-hepatic systemic blood. Rapid and extensive absorption and metabolism occurs following oral administration to rats and man. The applicant states that there was no evidence for inhibitory effects on the mixed function oxidase CYP3A4.

22. The applicant states that DHC cannot be accumulated in adipose tissue or the brain as it is readily metabolised to VOH and 8-MNA in the GI tract and is not itself absorbed systemically (the applicant has cited a recent study relating to this). The applicant has outlined a study (Bernard *et al.*, 2010) investigating the tissue distribution of a single oral dose (10 mg/kg bw) of ^{14}C-DHC in fasting rats together with the metabolic profiles for DHC both before and after enzymatic hydrolysis. Radioactivity was measured in the tissues for up to 24 hours. The applicant states that the results show that DHC is metabolised in a multistep process, initially to VOH and 8-MNA. Subsequently, the majority of VOH is conjugated to glucuronate or sulphate, with minor amounts oxidised to vanillic acid. The applicant states that because of the rapid and apparently complete breakdown of DHC in the GI tract, the observed systemic radioactivity came from the VOH metabolites/conjugates, due to radio-labelling of DHC.

23. Based on these study results, the applicant states that radioactivity in the brain (cerebrum) was below the limit of detection 24 hours after dosing so VOH apparently did not accumulate in the brain. Radioactivity was observed until 24 hours after dosing in adipose tissue (fat and brown fat) but the level decreased in parallel with that in the plasma (plasma half life was calculated to be 2.4 hours). Plasma T_{max} was achieved 40 minutes post dosing and the radioactivity declined thereafter. The applicant states that total excretion after 72 hours was 98.1% (78.2% urine, 19.4% faeces and 0.5% expired air). Residual radioactivity in the carcass (including GI tract and gall bladder) was 4% of the dose at 72 hours. The

applicant acknowledges that the metabolism of 8-MNA was not investigated in this study due to the position of the radiolabel but the applicant states that as 8-MNA is a mid-chain fatty acid, it is likely to be metabolised by mitochondrial or peroxisomal ß oxidation.

Toxicology – Animal and *in vitro* studies

24. The applicant has provided details of animal studies conducted on commercial grade DHC (the novel ingredient in the form to be marketed), laboratory scale DHC (an earlier form of the novel ingredient prior to scaling up) and CH-19 Sweet extract. The applicant has provided data to demonstrate that commercial grade DHC and the laboratory scale version complied with the specifications for DHC. The applicant has also provided specifications for CH-19 Sweet extract and shown that the Lots used as toxicological test material comply with these specifications.

25. Animal studies on commercial grade DHC are presented in the dossier. The applicant has provided details of 13 week and 26 week rat studies in addition to teratology and developmental toxicity studies in rats and rabbits. The applicant states that based on results from studies, DHC has a low acute oral toxicity (>5 g/kg), is well tolerated on repeat dose administration over 13 or 26 weeks by oral gavage, is non teratogenic and non-mutagenic or clastogenic in *in vivo* studies. The applicant concludes that these studies demonstrate an overall NOAEL of 1000 mg/kg bw/day. The only consistent changes observed were in the subacute and subchronic rat studies where slight weight increases in the liver and kidney were observed at the 1000 mg/kg dose, but in the absence of toxicity as evidenced by histopathological examination. The applicant acknowledges that small changes in alanine transaminase (ALT) were observed in individual animals but states that these were generally within normal limits for the age and sex of rats involved and for the contract testing facility. The applicant states that minimal or mild grade hepatocellular hypertrophy was seen in two high dose level male rats in the 13 week study, but was not seen in the 26 week study. In consequence, the high dose level in both the 13 week and 26 week studies was judged not to be toxic, thus providing a NOAEL of 1000 mg/kg. This NOAEL is 1300 times higher than the estimated high level intake by adult consumers (see paragraph 17 above).

26. The applicant has also provided data from gene mutation and mouse micronucleus studies and states that based on these studies DHC is not mutagenic or clastogenic.

27. The applicant has also provided details of toxicity studies conducted on laboratory scale DHC. The studies and results are summarised in the following table.

Study	**Author, study experiment No.**	**Result**

13-week oral gavage toxicity study in rats.	Mochizuki, M. 2006 N-B205	NOAEL >1000 mg/kg
Bacterial Reverse mutation test	Shimada, S. 2006 9612 (258-046)	Non mutagenic +S9, mutagenic in TA100 only in absence of S9.
In vitro chromosome aberration test	Masumori S. 2006 9613 (258-047)	Non-clastogenic +S9. Clastogenic only in absence of S9.
In vivo mouse micronucleus test	Nakajima M. 2006 9623 (258-048)	Non-clastogenic
In vivo Comet assay in rats	Shimada S. 2007 9993 (258-061)	Equivocal DNA damage, within historical control values.

28. As some of the toxicological studies revealed unexpected results relating to genotoxicity, the applicant carried out relevant follow-up *in vivo* studies which yielded negative results.

29. For completeness, the applicant has provided details of toxicity studies conducted on CH-19 Sweet extract, which contains 7.5% capsinoids of which ca. 20% is dihydrocapsiate. The level of dihydrocapsiate is identified for each study and a summary table to these toxicity studies is provided below:

Study	**Dihydrocapsiate dose equivalent (mg/kg)**	**Author, Study/experiment number**	**Result (mg/kg Dihydrocapsiate)**
Single dose acute oral toxicity tests in rats.	71.25 142.50 285	Mochizuki M. 2005	LD50 >285 mg/kg
13-week oral gavage toxicity study in rats	Low 16.63-20.19 Mid 33.25-40.38 High 66.50-80.75	Mochizuki, M. 2006a.	NOAEL 66.5 to 80.75*
26 week oral gavage toxicity study in rats	Low 16.63-20.19 Mid 33.25-40.38 High 66.50-80.75	Mochizuki, M. 2006b	NOAEL in males 33.25 to 40.38* NOAEL in females 66.5 to 80.75*
Oral gavage teratology and	Low 20.19	Katsumata Y. 2006a	Maternal and foetal NOAEL

developmental toxicity study in rats	Mid 40.38 High 80.75	N-R013	80.75
Oral gavage developmental toxicity study in rabbits	Low 3.8 Mid 7.6 High 15.2	Matsouka T. 2006 N-R010	Maternal and foetal NOAEL 15.2
Two generation oral gavage reproduction study in rats	14.25-20.19 28.5-40.38 57-80.75	Katsumata Y. 2006b N-R008	NOAEL 57 to 80.75*
Bacterial reverse mutation test	-	Nakajima. 2005 9224 (258-041)	Not mutagenic
In vitro chromosome aberration test	-	Masumori S. 2005a 9225 (258-042)	Not clastogenic
Mouse micronucleus test	-	Masumori S. 2005b 9226 (258-043)	Not clastogenic

*due to range of DHC content in different Lots of CH-19 Sweet extract

- plate concentration conversion in DHC equivalent not calculated.

Human studies

30. The applicant presented two human studies which showed that DHC administered in capsules at 3 or 12 mg volunteer/day for 8 days or in beverages at 3 or 9 mg volunteer/day for 4 weeks, was well tolerated and gave rise to no obvious dose related clinical signs or treatment related effects. The applicant stated that the occasional and sporadic findings recorded in the two separate studies seldom occurred in more than one volunteer/sign and there was no consistent pattern or trend. The side effects reported in the studies included stiff neck, high total cholesterol and blood urea nitrogen, constipation, bradycardia and loose stools. These studies also revealed some variations in blood pressure in DHC-treated individuals but the applicant concluded that these minor variations are unlikely to be related to treatment as increases were observed in one study and reductions in the other.

31. The Committee examined detailed reports of the human studies in relation to the apparent blood pressure-related changes that were observed and agreed that these were not a cause for concern.

32. The Committee requested additional information from the applicant on pharmacological and nutraceutical effects of DHC or its metabolites. Although efficacy assessment of a novel ingredient is not within the remit of the Committee's function, in this instance, Members felt this information would be useful in evaluating the safety of the product. The Committee was particularly interested in the interaction of DHC or its metabolites with vanilloid receptors in the mouth and gut and whether DHC or its metabolites may give rise to any cardiovascular or neurological effects.

33. The applicant explained that DHC interacts with vanilloid type-1 (TRPV-1) receptors on the tongue and provided background information on this family of proteins. TRPV-1 is a protein which is a member of the TRPV group of transient receptor potential family of ion channels and in humans is encoded by the TRPV-1 gene. TRPV-1 is a non-selective ion channel and may be activated by a wide range of exogenous and endogenous stimuli, the best known being heat greater than 43°C and capsaicin. The applicant states that both capsaicin and capsinoids interact with and activate TRPV-1 receptors in the same manner but the potential for interaction of DHC with oral TRPV-1 receptors is less than that for capsaicin.

34. The applicant also stated that DHC acts locally in the GI tract to activate TRPV-1 receptors. These receptors are expressed on the peripheral terminals of the primary sensory neurons such as the vagus nerve. The applicant cites a study to show that DHC is rapidly metabolised to vanillyl alcohol (VOH) and 8-methyl-nonanoic acid (8-MNA) in the GI tract and intact DHC is not absorbed in the systemic circulation. The applicant states that while both of these DHC metabolites are absorbed, neither is expected to have significant pharmacological activity or have any specific interaction with TRPV-1 receptors. The applicant states that there is no evidence to suggest that DHC can give rise to cardiovascular effects and has highlighted specific studies to reiterate this point. One study highlighted that a single oral dose of up to 30 mg of capsinoids (approx. 8 mg DHC) per person did not result in any increase in blood pressure/heart rate or any other clinically relevant effects in healthy volunteers. In another study, capsaicin supplementation (150 mg/person) one hour before exercise intervention had no effect on cardiac autonomic nervous system activities and cardiac electrical stability during exercise in obese individuals (the applicant states these findings can read across to DHC because it interacts with TRPV-1 receptors in the same way as capsinoids). A final study highlighted by the applicant to demonstrate the lack of any generalised response that could lead to cardiac involvement revealed that there were no significant changes in the levels of either plasma or urine catecholamines (adrenalin and nor-adrenalin) after ingestion of 30 mg/person of capsinoids (approx. 8 mg DHC/person). Catecholamine levels were measured at 15 and 30 minutes after ingestion, then again at 1, 2, 4, 8 and 24 hours for plasma and at 24 hours after ingestion for urine.

35. The applicant states that DHC only has local sensory effects and these are mediated via the TRPV-1 receptors on the surface of the GI tract, from the buccal cavity along the length of the gut. The applicant does however state that local activation of TRPV-1 receptors by DHC can impact both brown and white adipose sympathetic receptors through stimulation of the vagus afferent nerve and the sympathetic nervous system but not the heart.

***Discussion**: The Committee noted that the applicant had derived a NOAEL of 1000 mg/kg from the animal feeding studies conducted with DHC. The Committee considered that a NOAEL of 300 mg/kg would be more appropriate, but emphasised that a large safety margin still exists at the 300 mg/kg level.*

The Committee did not have any significant safety concerns relating to DHC. The Committee noted that DHC interacts in different ways with TRPV1 receptors along the GI tract and no further information was requested from the applicant on this issue.

The Committee requested further clarification of the applicant's statement that the metabolites of DHC (8-MNA and VOH) are not expected to have any pharmacological activity. The applicant explained that both metabolites have food uses[11] and no references have been found in the literature to indicate any significant intrinsic pharmacological activity. The applicant additionally stated that, taking into account the long history of safe use observed following natural systemic exposure to both substances from the traditional consumption of chilli peppers and, in the case of VOH, from vanilla (vanillin), together with the lack of any apparent pharmacological effects in the animal toxicology and human clinical trials with DHC there is an overall lack of evidence for any significant pharmacological activity of these two metabolites following oral administration. This comment excludes flavour as a 'pharmacological effect. Thus, while both are absorbed, neither metabolite is expected to have any specific interaction with TRPV-1 receptors.

The Committee was satisfied with the applicant's response.

XIV. Allergenicity and labelling

Information on this aspect is provided on p.74 of the application dossier

36. The applicant's view is that because DHC is synthesised and not extracted from plant material it is unlikely to cause IgE food related allergy. The only potential source of protein entering the production process would be from the lipase enzyme in the esterification reaction. The enzyme is immobilised in an inert carrier and cannot partition into the n-hexane fraction containing DHC. In the worst case scenario, even if granulate "fines" containing the immobilised enzyme entered the hexane layer, the particles would be trapped during filtration (filter porosity is 5µm) and would be separated from the DHC product. The applicant states that the enzyme manufacturer (Novozymes, Denmark) has conducted studies to illustrate that the carrier is robust under normal usage and there is no release of the enzyme or other materials.

37. The applicant additionally highlights that no allergic reactions have been reported in workers involved in production of DHC or CH-19 Sweet extract and, although peppers have been shown to cause allergy, there are no citations relating to any effects for DHC.

[11] VOH is a permitted food flavouring in the EU. 8-MNA is designated as a flavouring in Japan by the Ministry of Health, Labour and Welfare.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

CONCLUSION

The ACNFP has completed its assessment of DHC as a novel ingredient to be added to a range of foods and did not have any safety concerns relating to this ingredient. The Committee emphasised that its assessment was based purely on safety and it has not assessed or endorsed any health or taste benefits that have been suggested by the applicant. During its assessment of DHC, the Committee requested further information from the applicant on the following:

- The purpose of adding DHC to foods
- Pharmacological and nutraceutical effects of DHC or its metabolites
- Changes in blood pressure observed in the human tolerance studies
- Intakes.

After reviewing the applicant's response to these issues, the Committee did not have any outstanding safety concerns, although there was a degree of scepticism relating to the applicant's proposed reasoning for adding DHC to foods.

The ACNFP therefore concluded that DHC at the use levels proposed by the applicant will not present a health risk to consumers.

7 February 2011

(b) OPINION ON A TAXIFOLIN-RICH EXTRACT FROM DAHURIAN LARCH

Applicant **Ametis JSG**

Responsible Person **Inga Yegorova**

EC Classification **2.2**

Background

1. An application was submitted by Ametis JSG for authorisation of a taxifolin-rich extract as a novel ingredient in the EU, for use as an ingredient in a number of different food products.

2. Taxifolin, or (2R,3R) trans-dihydroquercetin, is a flavonoid extracted from the wood of Dahurian larch (*Larix gmelinii*), a species of larch native to eastern Siberia, adjacent regions of Mongolia and northeastern China. The product, which is obtained by hydro-alcoholic extraction of larch wood, has been marketed in Russia and the US for 15-20 years as a food supplement (e.g. a dietary antioxidant), and it is also authorised for as a food additive (preservative) in a wide range of foods in the Russian Federation.

3. The application is for authorisation of a taxifolin-rich extract which is referred to as "taxifolin" in this opinion. It has been 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.

4. The applicant has classified taxifolin as a pure chemical or simple mixture from non-GM sources where the source of the novel food has a history of food use in the EU (class 1.2).As it is questionable whether the source material has a history of use in the EU it would appear that Class 2 (a complex novel food from non-GM sources) may be more appropriate. However, as the information requirements for a submission for either class are the same, the risk assessment is unaffected.

I. Specification of the novel food

Dossier, p 7-15

5. The final product is composed of a minimum of 90% taxifolin (dry weight) together with a number of other identified and unidentified flavonoids (see para 7). The product specification is detailed below.

Parameter	Specification
Outward appearance	white or straw-colored powder
Moisture	10% max
Taxifolin (m/m)	90% min (dry weight)
Lead (ppm)	0.5 max
Arsenic (ppm)	0.02 max

Cadmium (ppm)	0.5 max
Mercury (ppm)	0.1 max
Dichlorodiphenyldichloroethane (DDT) & metabolites[1] (ppm)	0.05 max
Ethanol (ppm)	5000 max
Solvent residues, Class I	not detected (ND)
Solvent residues, Class II	not detected (ND)

[1] testing is a requirement of the Russian Federation

6. Batch on batch variation was assessed by analyses of 5 non-sequential batches. The results of these analyses showed that all batches analysed met the required specification criteria as set out and there was little variation between batches.

7. Although taxifolin is the dominant flavonoid both in *L. gmelinii* and the novel ingredient the applicant has also sought to identify other flavonoids that are present in the final product. The results from the same 5 batches are detailed in Table II.3.3-1 of the dossier and the mean values are given in the table below. Allowing for the internal standard used in the analysis, (0.8% caffeine) there are approximately 2.8% unidentified compounds which could include trace quantities of ethanol and saponins (<0.5%). In response to a request from the Committee regarding the nature of the unidentified components present in the extract, the applicant carried out a literature review which showed that plant based foods contain a wide range of flavonoids, which are not normally associated with any effects of toxicological significance. The applicant also noted that there is a number of foods which contain the identified flavonoids at significantly greater levels than those found in the novel ingredient.

Flavonoid Composition	
Taxifolin	92.36%
Aromadendrin (Dihydrokaempferol)	2.99%
Eriodictyol	0.198%
Quercetin	0.436%
Naringenin	0.26%
Kaempferol	0.06%
Pinocembrin	0.088%
Total	**96.4%**

Discussion *Noting that the source material was a plant source, the Committee was satisfied that the novel ingredient can be produced reproducibly by the applicant. The Committee accepted that there is a wide range of flavonoids present in plant based foods and that those present in the novel ingredient (identified or otherwise) were unlikely to give cause for concern. Given the reproducible nature of the product the Committee accepted the applicant's suggestion to increase the minimum level of taxifolin present to 90% dry weight (from 88%) in line with the specification used in the Russian Federation. The Committee agreed that, as the raw material was not subject to any herbicide or pesticide treatment there was no requirement to test for pesticide residues other than DDT, which was a mandatory requirement of the Russian Federation.*

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

Dossier, p 16-30

8. The specifications of the raw materials used in the production process are detailed in Table II.1.1-1 and Appendix C of the dossier. The source material, tree stumps of *L. gmelinii*, is first tested for heavy metals, a range of pesticides as well as microbiological load and radionuclides. Taxifolin is present in the source material at levels not less than 3.3% and the ethanol (96%) used in the extraction process complies with Directive 2009/32/EC concerning extraction solvents. The water used complies with the EU directive concerning potable water (Directive 98/83/EC).

9. The source material isdried to moisture levels of around 25%, debarked and ground to sawdust before hydro-alcoholic (75-85%) extraction of soluble substances at a temperature of 45-50°C. The extracting agent is distilled off and the sawdust returned for an additional alcohol extraction. After cooling to 20-25°C to remove resinous compounds the resulting aqueous phase is evaporated and crystallised and, after drying, contains a minimum of 90% taxifolin on a dry weight basis. Details of the quality control procedure employed by the applicant are detailed in the dossier (pp22-24 and Appendix D).

10. The applicant has assessed the stability of the novel ingredient using accelerated testing conditions, which indicate that the product is stable for at least 5 years when stored under 'normal' conditions. These are defined to be at temperatures above 4°C, 40-60% humidity, good ventilation and away from direct sunlight. The applicant does not comment on the stability of the product when added as an ingredient to other foodstuffs, nor is an indication of the proposed shelf life given.

Discussion *The Committee accepted that appropriate quality control procedures were in place for individual batches of the novel ingredient. Members noted that the applicant did not specify an upper storage temperature, and while testing under accelerated testing conditions indicated that the novel ingredient was stable for up to 5 years, the stability of the product in food matrices had not been tested. The Committee also noted that the environmental impact of producing the novel ingredient was minimal as the tree stumps were a by-product of the logging industry and trees were not felled solely for the purpose of its production.*

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

Dossier, p 30-34

11. A limited number of species from the genus Larix have food uses. Larch arabinogalactan from *Larix occidentalis* has gelling characteristics and is marketed as a food supplement, as a source of fibre and as a prebiotic. Other species in the genus (*Larix rossiea and Larix lacricinia*) are used in a range of herbal

remedies. There do not appear to be any other recorded food uses for *Larix gmelinii* and the applicant reports that there are no reported safety concerns attributed to its consumption.

Discussion *The Committee noted that there was limited use of Larix spp for food production purposes and that the uses described were for products that bear little resemblance to taxifolin (see comment on para 4 above)*

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

Dossier, p 34-46

12. The applicant intends that the novel ingredient will be incorporated into a relatively wide range of products and the level of addition is adjusted in accordance with the amount of fat present in the food.

13. Due to their similarity, not all the proposed products are shown in the summary table below but they are listed in full in the dossier (Table IX.1.1.-1).

Food Category	**Typical use**	**Use-Levels** ***(g/l or g/kg)***
Beverages	Concentrated soft drinks – not low calorie, as consumed	**0.02**
	Carbonated soft drinks – low calorie	**0.01**
Cereals and cereal & grain products	Biscuits	**0.07**
	Cereal Bars	**0.07**
	Energy and Diet Meal Bars	**2.144**
Meat	Ground meat	**1.389**
	Ground chicken	**2.616**
	Poultry sausage	**1.390**
	Coated and/or fried white fish (0.5 g/1 kg lipid mass - ca.10%)	**0.161**
Milk products	Dry milk, 15% fat	**0.161***
	Dry soy milk concentrate	**0.2***
	Curd desserts	**0.13***
	Yogurt	**0.050***

Sugar, Preserves, Confectionery	Chocolate confectionery	**0.030***
Fats and oils	Butter	**0.030***
PARNUTS*	Sport supplements	100mg
Food Supplement	Tablet or capsule	100mg (adult) 25mg (child)

* Foods for particular nutritional purposes

14. The applicant used published food consumption data from the UK National Diet and Nutrition Survey (NDNS) to provide a basic estimation of taxifolin consumption for the proposed range of products. The applicant did not explain in detail how the intake estimates for each of the food categories were calculated but provided 'worst case' and 'realistic' consumption based on the assumptions that either 100% or 10% of the products in an individual's diet will contain taxifolin. In order to estimate high level consumption the applicant has, based on literature surveys, assumed that intake at the 97.5th percentile is twice the mean figure.

15. Experts in food chemical intake from the Food Standards Agency advised that the assumptions noted above are not the usual approach, and that a better estimation of intake at the 97.5th%ile is three times the mean figure. However they also advised that the approach used by the applicant involved summing the high level exposure for each food category to give an overall figure for high level consumption. In practice would not be possible for the same individuals to be a high level consumer for every food category and this approach would inevitably lead to an overestimation of the likely level of consumption at the 97.5th%ile. As the calculated value was well below the proposed ADI for taxifolin (see Section XIII), it was not considered necessary to make a more refined intake estimation in this instance.

16. The summary table below summarised estimated intake levels for each population group detailed in the published NDNS surveys. The summary does not distinguish between male and females but, for adults, the all user data does not seem to differ markedly between the sexes. Very little additional data are provided for other age groups.

Age years (body wt)	ADI*	**All User data**			
		Mean daily intake:		97.5%tile daily intake:	
		mg	mg/kg body wt	mg	mg/kg body wt
1.5-4.5 (15 kg)	225 mg	33	2.2	65	4.3
4-10 (30 kg)	450 mg	43	1.4	86	2.9
10-18	825 mg	65	1.2	130	2.4

(55 kg)					
Adult (70 kg)	1050 mg	65	0.9	130	1.9

*See section XIII

Estimates do not include use in supplements and PARNUTs

17. These estimates do not include use either as a supplement or in foods for particular nutritional uses (PARNUTs) but the consumption of both at the maximum recommended level would be well within the adult ADI.

Discussion *The Committee noted the shortcomings in the approach used by the applicant to estimate intake, but agreed that it has led to a significant overestimation of likely consumption levels. As these intake estimates are well within the acceptable range, no further refinement is necessary in order to demonstrate safety.*

X. Information from previous human exposure or its source

Dossier, p 47-55

18. Taxifolin is marketed as a dietary antioxidant in a wide range of foods and the applicant is the world's major supplier of taxifolin, producing around 70% of the taxifolin sold in the Russian Federation. Ametis' taxifolin is available in a range of products (mainly food supplements, but also soft drinks, and fruit bars) marketed by a number of different companies. These companies are predominantly in Russia, but also the US and Switzerland. Approximately 250 products containing taxifolin have been registered in Russia (142 supplement products, 40 food products with the remainder being cosmetics) and the applicant alone has sold over 18 tons of taxifolin for use in food supplements.

19. The Russian Federation has approved the use of taxifolin both in food supplements (100mg/day) and as a food additive (preservative). However, the applicant has confirmed that the proposed uses described in the current dossier are solely for nutritional purposes (Dossier 1 Table IX1.1, and p35).

20. The companies who produce taxifolin in the Russian Federation maintain databases to record product return information. Ametis note that they are unaware of any recorded side-effects reported to the companies, nor is there any instance of product returns reported either to the producer or distributer.

21. Taxifolin is also present in the supplement Pycnogenol, a flavonoid preparation extracted from the bark of French Maritime Pine (*Pinus pinaster)*. This supplement has been on the EU market for over 20 years and contains a number of water soluble flavonoids including very small quantities of taxifolin (around 1.4mg per recommended daily dose). Although there are clear differences between taxifolin and the Pycnogenol product, the safety of the latter product was reviewed by the ACNFP in 1997 under the voluntary novel food review system which operated in the UK at that time. The ACNFP's concerns about poorly reported toxicological studies were referred to the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) for review. The COT also raised concerns about the quality of the data as many of the studies were either old or incomplete and also queried possible adverse effects seen in a 6 month canine study. As Pycnogenol had been on the market for many years in other EU countries it was subsequently found to fall outside the scope of the novel food regulation.

22. Small quantities of taxifolin are also seen in a number of commonly consumed fruit and vegetables, such as olive oil, red onions a range of citrus fruits and grapes

Discussion *The Committee accepted that there was evidence of consumption of taxifolin as a constituent of existing foods. Although ACNFP and COT previously raised questions about another flavonoid product, Pycnogenol, these are not relevant to the current evaluation as the two products have very different compositions.*

XI. Nutritional information on the novel food

Dossier, p 56-66

23. The applicant describes a number of perceived nutritional benefits that are attributed to the consumption of taxifolin. These include antioxidant effects, anti-inflammatory, anti-allergic properties and cardiovascular protection(Tables XI.2.1, XI2.2). The applicant notes that the studies cited in support of nutritional effects, in which 20-100mg/kg body weight of taxifolin was consumed, also demonstrate that it is safe and does not give rise to adverse effects (see also section XIII below).

Discussion *The Committee noted that the nutritional information supplied by the applicant largely relate to health claims. Such claims cannot be considered under the novel foods regulation but must comply with EU legislation on nutrition and health claims.*

XII. Microbiological information on the novel food

Dossier, p 67-69

24. The final product is tested to confirm the absence of a number of pathogenic microorganisms in accordance with the European Pharmacopeia. The microbiological specification for the product is detailed in Table XII.1-1, Appendix B and summarised below. Analysis of 5 batches demonstrated compliance with this specification.

Specification Parameter	**Specification**
Total Plate Count, TPC	NMT 10^4 CFU/g
Enterobacteria *	≤ 100/g
Yeast and Mold	NMT 100 CFU/g
Escherichia coli	Negative/1 g
Salmonella spp.	Negative/10 g
Staphylococcus aureus	Negative/1 g
Pseudomonas spp.	Negative/1 g

*Enterobacteria are only tested if the TPC exceeds 100 CFU/g.

Discussion*: Members accepted that the production process did not give cause for microbiological concern, and that compliance with the specification would ensure that the novel ingredient is free from pathogenic microorganisms. Given the nature of the raw material the Committee asked whether the applicant tested for the presence of mycotoxins. The applicant indicated that they did not routinely test for mycotoxins but the quality control (QC) systems that they employ in the selection of the raw material, coupled with routine*

testing for yeasts and moulds in the resulting sawdust, are adequate to ensure their absence. The applicant also carried out an analysis of one batch of the novel ingredient which showed that aflaxoxins were absent at the limit of detection. Members accepted that the QC systems appeared to be adequate but, in line with advice from Food Standards Agency officials who are responsible for the regulation of mycotoxins, noted that there is a wide range of mycotoxins that have adverse effects on human health and suggested that additional testing should be carried out during production.

XIII. Toxicological information on the novel food

Dossier, p 70-111

25. The dossier describes a number of relevant safety studies and, in response to questions raised by the Committee, the applicant confirmed that the sub-chronic and reproductive toxicity studies carried out by Dorovskikh and Celuyko, (2008) used their taxifolin product. Other studies had used taxifolin preparations from other manufacturers, using the same or very similar methods of extraction. The applicant also provided the specification of the taxifolin extract used by Shkarenkov *et al* (1998), who carried out a number of the toxicological studies cited in the dossier. This extract contained comparable amounts of taxifolin and other identified flavonoids to the applicant's product. Although other minor flavonoid components have not been identified, the applicant considered that these would not have any toxicological consequence due to their presence in a relatively large number of foods.

26. The applicant also noted that all taxifolin sold in the Russian Federation contained at least 90% taxifolin with the remaining 8-10% comprising other flavonoids such as dihydrokaempferol and naringenin.

27. Acute Studies (taxifolin from larch). Taxifolin toxicity was assessed following single administration (intraperitoneal or intragastric) to 60 rats and 80 mice. These studies brought about transient symptoms (shortness of breath, languor, cyanosis of skin augments of auricles and limbs) in a few animals indicating that the LD_{50} was in excess of 560-580 mg/kg.

28. Acute studies (taxifolin from other sources). Intraperitoneal administration of taxifolin to albino rats indicated an LD_{50} of 1200mg/kg.

29. Subchronic studies (taxifolin from larch). In a study carried out in 2008 (Dorovskikh and Celuyko), the applicant's product was administered orally (10g/kg body weight) to 20 rats for 7 days and no changes in the general condition of the animals were reported. In stage two of the same study 15g/kg body weight taxifolin was administered and no mortality was observed. Histological examination did not record any changes in the vital organs.

30. Chronic studies (taxifolin from larch) A 6 month study carried out in 1998 (Shkarenkov *et al*) using a comparable test material did not show any changes in the systemic condition of the rats (dose 150 and 1500mg/kg body weight/day). Slight changes in the leukocyte and thrombocyte levels were viewed to be within normal levels of variation. Biochemical examination of blood and of the functional state of the liver, kidneys and cardiovascular system showed no evidence of toxicity. A 6 month study also carried out in 1998 by the same authors but using dogs (dose 190/mg/kg body weight/day) also showed no visible effects on the behaviour of the animals whilst electrocardiograms, investigations into central nervous system activity and extensive biochemical analysis of blood, marrow, and excretory systems did not indicate any adverse effects of taxifolin.

31. **Chronic studies (taxifolin from other sources)** Two 6 month studies in albino rats (carried out in 1957) showed no adverse effects in any of the treatment animals.

32. **Developmental studies (taxifolin from larch)** In a 2008 study (Dorovskikh and Celuyko,2008) the administration of 0.5g/kg body weight of the applicant's product to rats over a 90 day period during gestation and in the postnatal period did not result in any visible changes in the behaviour of the animals and there no toxicosis or pathological reactions were seen. No changes were seen in newborns in the developmental and growth stages and histological examination did not report any changes in the heart, liver, spleen, kidneys, stomach, small and large intestine, cortex and spinal cord. Shkarenkov *et al* (1998) administered taxifolin (75 and 1500mg/kg body weight by i.p. injection) to 75 rats in each of the first 19 days of pregnancy. The same report also investigated the effect of taxifolin on the reproductive function of both male and female rats. Although some minor changes were seen in the haemapathological indices of newborn rats these were judged to be within normal ranges and the authors concluded that taxifolin had no effect on the reproductive function of the rats.

33. **Developmental studies (taxifolin from other sources)** a transcriptional activation assay carried out in cell culture found no effect on the oestrogen receptor. Although a very low measure of oestrogenicity was observed in morphological and biochemical assays there was no significant effect on the induction of lactoferrin. Another study with rat uterine cytosol showed that taxifolin does not bind to the uterine cytosolic oestrogen receptor.

34. **Mutagenicity and genotoxicity (taxifolin from larch).** Studies evaluating chromosomal aberrations of mice bone marrow cells showed that the administration of 1500mg/kg of taxifolin had no effect indicating a lack of mutagenic properties. *In vivo* genotoxic effects were studied using chromosomal aberration and DNA-comet assay methods. No DNA damage in the blood, liver or rectal cells of mice were seen

35. **Mutagenicity and cytotoxicity (taxifolin from other sources).** The mutagenicity of taxifolin (and other flavonoids) was assessed using an Ames test and was found to be non-mutagenic. A number of other mutagenicity studies are also detailed in the dossier and non give any indication that taxifolin would be mutagenic. Cytotoxicity studies using human lung embryonic fibroblasts and umbilical vein endothelial cells, and also rat hepatocyte and HeLa tumor cells showed weak toxicity at high concentrations of taxifolin.

36. **Acceptable Daily intake** The applicant has sought to determine an Acceptable Daily intake based on the toxicological studies reported above. Noting that it is difficult to determine a no observable adverse effect level (NOAEL) because large doses of taxifolin (e.g. >1500mg/kg bodyweight in the 6 month oral toxicity study in rats) do not give rise to any adverse reactions. However based on the highest dose used in this study and applying a standard safety factor of 100, the applicant suggests that the ADI should be 15/mg/kg body weight.

37. **Absorption.** The results of absorption studies carried out on taxifolin (from larch wood) are detailed in Table XIII.2-1(p88 of the dossier). A 2009 study (Pozharitskaya *et al, 2009)* indicates that the bioavailability of taxifolin (36%) is higher in rabbits when consumed in lipid solution than in tablet form. In a separate study, trace amounts of taxifolin were detected after oral administration and, when compared with intravenous administration, a bioavailability figure of 0.17% was calculated. Intravenous injection to rats at levels up to 30mg/kg showed non-linear pharmacokinetic behaviour, and oral administration resulted in taxifolin being seen in the plasma only at trace levels. The pharmacokinetics of a single dose of taxifolin in 8 male rats show a rapid absorption from the GI tract, reaching a maximum concentration in the blood plasma after 30 min, and undetectable levels after 8h. The study authors

(Seredin *et* al, 2007) viewed taxifolin to be a short lived product and the bioavailability was calculated to be around 23%.

38. **Distribution.** The same 2007 study also reviewed distribution indicating that taxifolin was detectable in the blood plasma, liver heart, spleen, brain skeletal muscles, lungs and kidneys for up to 24 hours after administration. Higher quantities were found in the kidneys whilst the low quantities seen in vascularised organs are indicative of low permeability.

39. **Metabolism.** A 1983 study (Voskoboinikova *et al*) reported the conversion of taxifolin to 3' or 4'-O-methyltaxifolin in rats. A study from the 1950's using two human volunteers consuming 2g of taxifolin reported its conversion to a number of hydroxyphenylacetic acids. Seredin *et al*. (2007) reported a number of taxifolin metabolites in the urine of rats, predominantly derivatives of diastereomers of taxifolin.

40. **Excretion.** HPLC analysis of rat urine by Seredin *et* al, (2007) found a number of peaks which corresponded to the metabolites reported above. The authors report that around 8% of the original dose (50mg) was seen in urine during the first 24h after administration, but none was seen in the urine or faeces in the following 24h indicating complete absorption into the blood system. In a separate study (Voskoboinikova*et al.,* 1993) the excretion of taxifolin over a 24h period did not exceed 6% of the dose administered, with a near linear increase with dose. The authors suggest that the contribution of the kidneys is of little significance as the majority of elimination takes place via a metabolic pathway.

41. **Human Studies.** No adverse effects have been reported in a large number of studies in which taxifolin (from larch) was administered to patients with a relatively wide range medical conditions, including atherosclerosis, arterial hypertension, ischemic heart disease, discirculatory encephalopathy, diabetes, Lyme disease, patients awaiting operations on ovaries and chronic pulmonary obstructive diseases (pp95-101 and table XIII.2.7-1 in the dossier). The applicant notes that at total of 507 patients were treated with taxifolin (40-120mg/day) for 2 weeks to 3 months and no side effects were reported.

Discussion *In regard to the test material used in the safety studies, the Committee accepted a sufficient number of studies had been carried out using the novel ingredient, or a comparable counterpart, providing sufficient reassurance that it did not present a risk to consumers at the levels proposed by the applicant. The Committee noted the studies had been carried out to the standards of Good Laboratory Practice implemented by the Russian Federation.*

Allergenicity

Dossier, p 72

42. Although the absence of protein in taxifolin has not been confirmed experimentally, the applicant notes that the production process would be unlikely to result in any measurable protein in the final product. Although there are no reports of allergy to taxifolin, the applicant acknowledged that, as allergy to birch pollen occurs, it is conceivable that there could be allergy to larch pollen, although the production process would appear to rule out any possibility of non-denatured pollen in the final product. Potential allergenicity was investigated in a range of tests involving guinea pigs, which indicated that taxifolin did not give cause for concern in terms of hypersensitivity and anaphylaxis.

Discussion *The Committee accepted that there was little likelihood that taxifolin would pose an allergenic risk to consumers*

Overall Discussion

The Committee considered that the toxicological studies on Ametis' taxifolin product, and on comparable products, provided sufficient reassurance that the novel ingredient was safe for the proposed uses. With regard to potential intake, the Committee questioned the simplistic approach used by the applicant, but accepted the view of FSA officials that this approach provided an overestimate of the likely level of intake and concluded that these estimates provided a significant margin of safety for all population groups. The Committee also advised that the applicant should carry out regular testing to ensure that the final product is free from mycotoxin contamination. Although the precise frequency of this testing could be determined by the applicant, they should also ensure that this takes into account the range of yeast and moulds which could be introduced at each stage of production, either via the raw materials or during storage.

CONCLUSION

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant, Ametis, that the range of uses for the novel ingredient (Taxifolin Rich Extract from Dahurian Larch) is acceptable subject to the applicant's adherence to the proposed specification and the implementation of quality control measures described above and in their application dossier.

August 2011

(c) OPINION ON AN APPLICATION UNDER THE NOVEL FOOD REGULATION FOR PHOSPHATED DISTARCH PHOSPHATE AS A FOOD INGREDIENT

Applicant: **MGP Ingredients**

Responsible Person **Dr Ody Maningat**

EC Classification **2.1**

Background

1. An application has been submitted by MGP Ingredients for the authorisation of a phosphated distarch phosphate produced from wheat starch as a novel food ingredient in a range of low moisture food products.

2. Phosphated distarch phosphate is a chemically modified resistant starch derived from high amylose vegetable starch. Resistant starch (RS) is commonly defined as "the sum of starch and products of starch degradation not absorbed in the small intestine of healthy individuals". RS is divided into four types and Phosphated distarch phosphate is classified as a type 4 resistant starch (RS4). This classification covers chemically modified starches, which are the most resistant forms of modified starch. The novel ingredient contains a minimum of 66% dietary fibre (as measured by the AOAC method) and not more than 0.4% residual phosphorus, which is covalently bound to the starch molecules.

3. Phosphated distarch phosphate is currently listed as an approved food additive (E1413)[12] for use *quantum satis*[13]. This approval applies only to its use for technological purposes and E1413 is currently used in products such as soups, sauces, gravies and fruit fillings as a freeze-thaw-stable thickener. The use of Phosphated distarch phosphate for nutritional purposes is a new development and is therefore subject to the Novel Food Regulation (EC) 258/97.

4. This application for authorisation 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. Phosphated distarch phosphate has been classified as a complex novel food ingredient from a non-GM source having a history of food use in the community (class 2.1).

[12] European Parliament and Council Directive No 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners (as amended)

[13] maximum level not specified, in accordance with good manufacturing practice at a level not higher than it is necessary to achieve the intended purpose

5. This is the second application for the authorisation of phosphated distarch phosphate that has been considered by the Committee[14]. In 2009 the Committee completed its assessment of a similar phosphated distarch phosphate product derived from maize starch[15]. This assessment highlighted concerns regarding potential gastro-intestinal (GI) intolerance in children and concluded that there should be an accompanying advisory statement on all products containing the product.

6. As there are significant similarities between these two applications, this opinion is broadly similar, and has the same conclusions as that issued in April 2009.

I. Specification of the novel ingredient (NI)

Dossier p 11 – 19, Annex I-A, and I-B

7. The application is for two slightly different preparations of phosphated distarch phosphate which will be referred to as the novel ingredient (NI) with reference to the amount of RS-4 present (i.e. 66% or 76%) where it is necessary to distinguish between the two forms.

8. Although the specification for the NI given in Table I-2 of the dossier contained a number of inconsistencies, the specification detailed below has been amended to take account of these and is consistent with those seen for the previous application.

9. The applicant also carried out a routine analysis the raw material (wheat flour) for heavy metal, pesticide and mycotoxins and the analytical limits are detailed in Table 1-5 (p18) of the dossier and Annex 1-B. The applicant does not provide any analysis of individual batches of the NI, but has provided Technical Data Sheets which are supplied to customers (Annex 1-A) and these provide reassurance that the NI is produced within specification.

Company specifications for two phosphated distarch phosphate products made from wheat starch

Analyte	Description		Method	Frequency
	Fibersym®	FiberRite®		
Compositional (Dry basis)				
Phosphated Distarch Phosphate	85%	75%	AOAC 991.43	Every Lot
Unmodified Wheat	15%	25%		

[14] Application from National Starch – see http://www.food.gov.uk/multimedia/pdfs/phosphateddistarchphosphate.pdf
[15] http://www.food.gov.uk/multimedia/pdfs/pdpfinalopinionapril09.pdf

Company specifications for two phosphated distarch phosphate products made from wheat starch

Analyte	Description		Method	Frequency
	Fibersym®	**FiberRite®**		
Starch				
Physical				
Appearance	Fine Powder	Fine Powder	Visual	Every Lot
Colour	White to off white	White to off white	Visual	Every Lot
Odour	None	None	Sensory	Every Lot
Chemical				
Residual phosphorus	Not more than 0.4%	Not more than 0.4%	AOAC 995.1	Every lot
Arsenic	Not more than 1 mg kg^{-1}	Not more than 1 mg kg^{-1}	SW-8466010B R2.0	Annually
Lead	Not more than 2 mg kg^{-1}	Not more than 2 mg kg^{-1}	SW-8466010B R2.0	Annually
Mercury	Not more than 0.1 mg kg^{-1}	Not more than 0.1 mg kg^{-}	SW-8467471A R1.0	Annually
PH (25% slurry)	4.5 – 6.5	4.5 – 6.5	PRL002 – pH meter	Every Lot
Ash	Not more than 3%	[1]	AACC 08-03	Every Lot
Nutritional data (g per 100g)l				
Moisture	10.6	12.5	PRL019 Mettler moisture meter	Every Batch
Energy (Calories)	56.0	85[.4]		
Total Dietary Fibre	76.0	65.6	AOAC 991.43	Every Batch

Company specifications for two phosphated distarch phosphate products made from wheat starch

Analyte	Description		Method	Frequency
	Fibersym®	**FiberRite®**		
(dry matter basis)	(minimum)	(minimum)		
Ash	0.99	1.17	AACC 08-03	Nutritional Sample
Protein	0.5%	0.5%	LECO Combustion	Nutritional Sample
Total fat	0.50	0.34	GC	Nutritional Sample

***Discussion**: The Committee was satisfied with the additional information provided by the applicant on the specification of the NI and accepted that the compositional data show that it is reliably produced within the defined specification.*

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

Dossier p.19-22, Annex II-A

10. The starting material for the production of the NI is a starch slurry mixture derived from wheat starch (Figure II-1 of the dossier). Wheat starch is widely used in the food industry and the starch used in this instance is produced by the applicant. The starch is treated with sodium tripolyphosphate and sodium trimetaphosphate under alkaline conditions and with mild heating (47°C). The resulting slurry is then adjusted to pH 6, and is then dried to produce a final product with 76% fibre, or heat treated to produce a version containing 66% (See also Section XI below). The production process yields products which are within the EU specification for production of phosphated distarch phosphate for additive purposes.

11. In response to a request from the Committee the applicant provided information regarding the stability of the products. The applicant investigated changes in moisture content and total dietary fibre and used infrared spectroscopy to identify changes in the physico-chemico structure of the carbohydrates. These studies found no substantive change in either form of the NI during a 2-5 year storage period.

12. The production of the NI is in accordance with Hazard Analysis Critical Control Point (HACCP) procedures (Dossier, Confidential Annex II-A).

***Discussion**: The Committee noted that the production process of the NI is similar to that of the approved food additive phosphated distarch phosphate (E1413). Members accepted that there were appropriate controls in place on the production of the NI to ensure the safety of the final product. Although the applicant did not provide any data examining the stability of the NI in food matrices, Members were reassured by the analyses carried out by the applicant to demonstrate the stability of the NI over an extended time period.*

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

Dossier p.22-24

13. The applicant notes that the source material, wheat, is a widely available and extensively consumed commodity crop which has been subject to intensive breeding for many years. The applicant highlights that new varieties require a degree of scrutiny before they can be used commercially and notes that although there are few concerns about the safety of wheat *per se*, there are certain sets of the population for whom wheat is contra-indicated (see section XIII below).

***Discussion**: The Committee noted that there is a substantial history of consumption of wheat, the source used to produce the NI.*

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

Dossier p.24-34

14. The applicant is proposing to market the NI as a source of dietary fibre and as a replacement for flour in a relatively diverse range of foods. The applicant has not specified whether the introduction of the foods containing the NI will be restricted geographically. The applicant originally proposed that the NI be incorporated into a wide range of products including bread products, breakfast cereals, pasta biscuits and cakes at levels of up to 15%. Based on these proposed use levels, the applicant used data from a number of UK National Diet and Nutrition Surveys (NDNS) to estimate the anticipated daily intake of NI and residual (bound) phosphorus for the different population groups, in the EU. Although these data were viewed by the Committee to provide a reasonable estimate of consumption of the NI, as the applicant intended to incorporate the NI into a different range of foods to those proposed by the company responsible for the first application (see para 5 above), the Committee noted that an estimation of intake from these food groups was required to determine the potential level of consumption of phosphate distarch phosphate from all dietary sources.

15. As a result the applicant subsequently amended their proposed food categories to mirror those proposed in the earlier application, as shown in the following table.

Amended proposed food uses and use levels for NI and the corresponding levels of added phosphorus			
Food Category	**Proposed Food Uses**	**Maximum Use Level (%)**	**Added Phosphorus (1) (%)**
Cereals and Cereal Products (including bakery products)	Batters and breading	15	0.06
	Biscuits (sweet)	15	0.06
	Cakes and Muffins	15	0.06
	Pizza Dough	15	0.06
	Breakfast / nutritional / energy bars	15	0.06
Crisps and Savoury Snacks	Savoury biscuits, crackers and non-extruded snacks	15	0.06
Pasta and noodles	Canned pasta	15	0.06
	Pasta contained in ready meals	15	0.06

(1) Assuming a maximum of 0.4% of residual phosphorus

16. An intake assessment was carried out for these food uses by the original applicant who estimated that the mean daily intake of the NI will vary between 4.9 g/person (0.07 g/kg bw) for adult women and 9.0 g/person (0.17 g/kg bw) for male teenagers and high level daily intake will vary between 14.2 g/person (0.22 g/kg bw) for adult women to 25.3 g/person (0.53 g/kg bw) for male teenagers. On a body weight basis, the highest estimated intake is in young children (mean 0.38 g/kg bw/day, high level 1.09 g/kg bw/day). In practice, it is unlikely that these "worst case" intakes will be reached as it would necessitate the incorporation of the NI at the maximum level in all staple "starchy" foods.

***Discussion**: The Committee accepted that their previous view regarding estimated intake applied for the NI. The Committee previously noted that exposure to the NI was within the range tolerated*

in clinical studies (1 g/kg bw/day), with the exception of high level intake in small children. While there is a degree of conservatism in the calculation of these intake estimates, the potential for high levels of intake by young children requires careful consideration (see section XI below).

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

Dossier p.34-37

17. The applicant notes that the NI is permitted as a food additive in the EU and although they are of the view that there are no available data quantifying consumption as a food additive in the UK, the previous applicant noted that the current consumption of the additive E1413 is less than 0.5g/day.

The applicant also cites UK Government data which states that average daily starch consumption is 156g per person, equating to 26.4% of a daily diet. ***Discussion****: The Committee accepted that there was evidence that the NI had been consumed as a food additive in the EU.*

XI. Nutritional information on the novel food

Dossier p.37-50, Annexes XI-A,B, C and D

18. The applicant provided a detailed overview of the chemistry of starch and resistant starch. This aspect is covered in the previous application and is therefore not reproduced in this paper. Three studies which have been carried out by the applicant and were therefore not reported in the earlier application are detailed below.

    a) The applicant highlights an *in vitro* fermentation studied carried out on the NI (76%) comparing production of short chain fatty acids with a potato based resistant starch and the results of an earlier (1990) report which looked at a number of different starches. (Dossier, p45-46 and Annex XI-A). The applicant is of the view that, allowing for variation seen as a result of the two studies being carried out separately, the profiles are comparable, although there were some differences in the proportion of butyrate.

    b) The applicant reports a relatively old in vivo study where 12 healthy volunteers were fed 60g of a maize-based Phosphated distarch phosphate over 4 successive days with no adverse reactions. This study (Pieters *et al.,* 1971) was also reported in the previous application. To confirm these findings the applicant has carried out an additional human tolerance study using their NI (76%) (Dossier, p46-47 and Annex XI-B). In this study 10 young adults consumed 30-33g of a range of resistant starches including their NI (76%) every day over three 3 week periods. The applicant reports the study as showing no adverse reactions other than a mild increase in flatulence which was associated with consumption of resistant starch. Although some subjects showed significant differences in the profile of faecal bacteria the possible consequences of this are not considered.

    c) The applicant has also carried out a study to assess the effect of the NI (76%) on the glycaemic and insulinaemic response of healthy individuals (Dossier p 47-48 and Annex XI-C,

D) and monitored plasma insulin and glucose following consumption of muffins and cereal bars containing the NI. When incorporated into muffins, the NI had a greater effect on postprandial insulinaemia than it did on parallel measurements of glycaemia, while the reduction in glycaemia was greater when the NI was added to cereal bars. The applicant notes that similar matrix effects have been reported with other resistant starches.

19. Based on the results of these studies and others in cited from the scientific literature the applicant is of the view that the NI behaves no differently from naturally occurring resistant starch (RS1 & RS2) and resistant starch which is formed by cooking (RS3).

***Discussion**: The Committee agreed that the points raised in their consideration of the earlier application applied directly to this NI. These were as follows:*

A review article by Nugent, (2005)[16] investigated the health properties attributed to the consumption of resistant starch. This review summarises reports in the literature that indicate that the regular consumption of high levels (>30 g/day) of resistant starch may give rise to intolerance.

Although Members agreed that the human study carried out by the applicant together with an unpublished human study by Pieters et al., (1971) provided reassurance that the consumption of up to 60g of the NI per day would not give rise to GI significant intolerance in healthy adults, they questioned whether this conclusion could be extended to other population groups such as children, in whom gut microflora is still developing and does not have an adult composition until the age of about 11 or 12. Also, it is known that children are more sensitive than adults to the laxative effects of other poorly absorbed ingredients such as polyols.

Members noted that there are ongoing discussions at international level regarding the definition of 'fibre', independent of this application. The current UK advice, based on the view of the Scientific Advisory Committee on Nutrition is that the quantification of dietary fibre (for nutrition labelling purposes) should be carried out using AOAC methodology, a method that includes resistant starch in the definition of fibre. However, the UK currently advises that, for the purpose of health claims, the term "fibre" means non starch polysaccharides and excludes chemically modified resistant starch.

In practical terms this means that food manufacturers in the UK could include the contribution of the NI in the declared fibre content for nutrition labelling purposes, but could not refer to 'fibre' in the context of dietary or health claims. Until health claims are harmonised at EU level, products marketed in other EU member states have to comply with the relevant national rules concerning nutrition and health claims.

[16] Nugent, A.P. 2005. Health properties of resistant starch. Nutr Bull BNF 30:27-54.

XII. Microbiological information on the novel food

Dossier pp.15-17 & 50-51

20. The production of the NI does not involve the use of microorganisms and the manufacturing process is controlled through HACCP procedures

21. The applicant addresses issues of microbiological purity in the specification section (Appendix 1 p18), and also reports the results of a microbiological analysis of both forms of the NI (five independent batches), all of which were found to be within specification. The microbiological specification is as follows:

Table I-2 Company specifications for two phosphated distarch phosphate products made from wheat starch

Analyte	Description		Method	Frequency
	Fibersym® RW	**FiberRite® RW**		
Microbiological				
Aerobic plate count	10,000 cfu/g max	10,000 cfu/g max	FDA-BAM 8th Ed Rev.A Ch. 3	Every Lot
Moulds & Yeasts	200 cfu/g max	200 cfu/g max	FDA-BAM 8th Ed Rev.A Ch. 18	Every Lot
Escherichia coli	Negative	Negative	FDA-BAM 8th Ed Rev.A Ch. 4	Every Lot
Salmonella spp.	Negative	Negative	AOAC 990.13	Every Lot

cfu = colony forming units

***Discussion**: Members accepted that the production process did not give cause for microbiological concern, and that the compliance with the specification would require the NI to be demonstrably free from pathogenic micro-organisms.*

XIII. Toxicological information on the novel food

Dossier p.51 - 73

22. The applicant notes that as the NI is an authorised additive it has undergone an extensive safety evaluation in the EU. The applicant reports a large number of studies which were similarly reported in the previous application (See para 5 above) and are not summarised here.

Discussion:

The Committee agreed that the points raised in their consideration of the earlier application applied directly to this NI. The Committee therefore accepted that the available toxicological data provided adequate reassurance that the NI was not toxic. The human study by Pieters et al., (1971) provided reassurance that the proposed uses of the NI would not give rise to GI intolerance in healthy adults but the Committee questioned whether these results were applicable to high level consumption in young children (See section XI above).

Allergenicity and labelling

Dossier p.73-4

23. The applicant accepts that wheat is known to make a significant contribution to adverse reactions to food and acknowledges that the NI will have to be labelled in accordance with EU labelling requirements. The applicant states that the NI would not contribute any greater risk to wheat intolerant consumers than other commercially available wheat starch already used in the food industry.

24. The applicant acknowledged the concerns raised by the Committee regarding consumption by children highlighted in the previous application also apply to their products (see XI discussion, above) and in line with the Committee's conclusion regarding this issue (see footnote 4) proposes that they should include an advisory label to the effect that it may cause laxative effects in young children.

Discussion

The Committee accepted the applicant's view that, as an ingredient obtained from wheat, it is unlikely that the product presented any greater allergy risk to consumers than the source material and that it will be labelled in accordance with EU labelling requirements.

In line with the previous application the Committee noted that the use of a name such as "resistant modified (wheat) starch" would be appropriate for the NI and would be in line with EU food labelling regulations.

In its 2009 opinion (see paragraph 5,above) the Committee welcomed an applicant's intention to include an advisory label regarding possible GI intolerance noting that "this statement should clearly indicate that consumption of the NI may cause laxative effects in small children." Following a number of reasoned objections by other EU Member States, this application was referred to the European Food Safety Authority (EFSA) for additional assessment. EFSA recently issued a positive opinion on the safety of the product[17] which states that that there was no evidence to justify the mandatory inclusion of such an advisory label.

This Committee has considered the EFSA opinion[18] and although Members do not accept this position they agreed to amend their suggested statement to "may cause altered bowel habits". In coming to this view the Committee noted that, as many of the food categories would be attractive to, and consumed by, children, it should be possible for an applicant to gain ethical approval to carry out a limited and non-invasive study to determine the level at which consumption of the NI by children gives rise to intolerance. However until these data were available it was prudent to require an advisory statement on all foods containing the NI.

In line with the previous application the Committee also remains of the view that the applicant should consider the provision of additional information to ensure that the consumer is fully informed as to the nature of the NI. This could be achieved via a reference to a website and a manufacturer's careline.

Overall discussion

The Committee advised that issues of concern which were raised in the previous opinion (see para 5) were also applicable to this product. The Committee noted that the NI was an authorised food additive and, on this basis, accepted that it was unlikely to give rise to any toxicological concerns. However, Members expressed concern that use as an additive was at levels significantly lower than that proposed in this application. Although data were provided to demonstrate that the NI would not give rise to gastrointestinal intolerance in adults at the proposed levels of consumption, The Committee was concerned that a number of the proposed food categories would clearly be consumed to some extent by children, even if adults were the primary target for products containing the NI.

The Committee noted that, as a chemically modified starch, the NI was unlikely to be fermented by gut bacteria in the same manner as other classes of resistant starch. By comparison with other forms of resistant starch, it seems likely that a higher proportion of RS4 (chemically modified) starch would reach the large intestine, as a result of its lower digestibility, and it is also possible that its influence on bacterial fermentation would extend further along the colon. This makes it difficult to predict the consequences of consumption in all groups of consumers with confidence. In view of this, and mindful that unexplained digestive disturbances in children are an increasingly

[17] http://www.efsa.europa.eu/en/efsajournal/pub/1772.htm
[18] ACNFP101/5

common cause for concern among parents and physicians, the Committee concluded that all food containing the NI should carry an accompanying advisory statement for children.

CONCLUSION

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant, MGP ingredients that the range of uses for the novel ingredient (Phosphated Distarch Phosphate) is acceptable subject to the labelling requirement described above.

August 2011

(d) OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR ROOSTER COMBS EXTRACT

Applicant: **Bioiberica S.A.**

Responsible Person: **Laura Vicente**

EC Classification: **2.1**

Introduction

1. An application was submitted to the Food Standards Agency in February 2011 by Bioiberica S.A. for the authorisation of rooster combs extract (RCE) as a novel ingredient in the EU. A copy of the application was placed on the Agency's website for public consultation.

2. Rooster combs have been consumed in Europe as part of traditional dishes. RCE is an extract rich (60-80%) in sodium hyaluronate (SH) which is found in the intracellular matrix of animal and human connective tissues e.g. rooster combs. The applicant states that SH helps in lubricating and cushioning joints.

3. In addition to SH, RCE also contains glycosaminoglycans (approx. 20%) and partially hydrolysed proteins (approx. 20 %). Glycosaminoglycans are long unbranched chains of polysaccharides made up of repeating disaccharide units. The hydrolysed proteins are polypeptides, peptides and amino acids obtained by the hydrolysis of the proteins in the extract e.g. hydrolysed collagen.

4. Hyaluronate is synthesised naturally in the human body. The applicant mentions that foods containing SH are very limited and only rooster combs and viscera have high amounts of this substance. These sources of SH are not consumed in all European countries and the applicant therefore proposes to incorporate RCE into different foods which are consumed daily in Europe as a way of providing additional sources of SH in order to support joint health in the general population.

5. RCE has been classified as a complex novel food from non-GM source, the source of the novel food has a history of food use in the EU (class 2.1) according to the scheme in Commission Recommendation 97/618 (EC).

I. Specification of the novel food

Information on this aspect is provided on p. 11-21 of the application dossier

6. The chemical and physical specification for RCE has been established by the applicant and can be found in the table below.

SPECIFICATIONS	LIMITS	METHODS
Glucuronic acid content (expressed as sodium hyaluronate)	60 - 80 %	Eur. Ph. Monograph 1472
Appearance	White or almost white hygroscopic powder	Visual
pH	5.0 – 8.5	Eur. Ph. 2.2.3
Chlorides	Not more than 1 %	Mohr Method
Nitrogen	Not more than 8 %	Eur. Ph. 2.5.9
Loss on drying	Not more than 10 %	Eur. Ph. 2.2.32
Heavy metals	Not more than 10 ppm	USP <231>
Mercury	Not more than 0.10 ppm	Eur. Ph. 2.2.58
Arsenic	Not more than 1 ppm	Eur. Ph. 2.2.58
Cadmium	Not more than 1 ppm	Eur. Ph. 2.2.58
Chromium	Not more than 10 ppm	Eur. Ph. 2.2.58
Lead	Not more than 0.5 ppm	Eur. Ph. 2.2.58
Dioxins and furans	Not more than 2.0 pg/g	EPA* Method 1613
PCB's	Not more than 4.0 pg/g	EPA* Method 1613
MICROBIOLOGICAL PARAMETERS		
Total viable aerobic count	Not more than 10^2 cfu/g	Eur. Ph. 2.6.12

Escherichia coli	Absence/ g	Eur. Ph. 2.6.13
Salmonella sp.	Absence/ g	Eur. Ph. 2.6.13
Staphylococcus aureus	Absence/ g	Eur. Ph. 2.6.13
Pseudomonas aeruginosa	Absence/ g	Eur. Ph. 2.6.13

7. The applicant has provided data from analyses carried out on ten independent lots of RCE (Annex 1, p16-17) which demonstrate that all lots conformed with the specifications. Some parameters e.g. specific heavy metals (mercury, arsenic, cadmium, chromium and lead), dioxins, furans and PCBs were not analysed for every single batch, as the applicant states that the safety and quality of RCE is well established and the analysis of these parameters is done only twice a year to assure that these substances are absent. However, no less than three batches were analysed for each specification parameter.

***Discussion**: The Committee did not raise any concerns relating to this section of the dossier.*

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

Information on this aspect is provided on p 22-34 of the application dossier

8. RCE is produced by an extraction process from rooster combs, using enzymatic hydrolysis and subsequent concentration and precipitation of the product.

9. The production process is detailed in the dossier (Annex 1, p22-25, protected information).

10. Studies under accelerated storage conditions (40 ± 2ºC / 75 ± 5% Relative Humidity, RH, for 6 months) and long-term storage conditions (25 ± 2ºC / 60 ± 5% RH, 40-43 months) have been conducted with three different production batches of RCE. The applicant states that storage under these conditions, using as a primary packaging a triple LDPE bag, and a metal drum as a secondary packaging, did not compromise the stability of the RCE.

11. The stability of different concentrations of RCE in yoghurts was assessed under refrigerated storage conditions for 1 and 1.5 months, which covers the mean shelf life of a standard commercial yogurt (normally three weeks). Analyses show that RCE remained stable with only minor variations in concentration, which according to the applicant are considered acceptable, compared to the initial theoretical concentration. Moreover, the presence of the RCE did not cause any microbiological presence after 1.5 months.

***Discussion**: The Committee did not raise any safety concerns regarding the production process. The issue of animal welfare during the production of RCE was raised during the public consultation and also by the Committee. The applicant has clarified that rooster combs are obtained from authorized slaughterhouses that slaughter poultry for human consumption. Combs are obtained post-mortem from poultry that undergo ante and post-mortem veterinary controls and are declared as fit for human consumption. The applicant has provided a certificate from the*

slaughterhouse where the combs are obtained. The Committee was satisfied that there are no outstanding concerns relating to animal welfare.

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

Information on this aspect is provided on p 35-36 of the application dossier

12. RCE is obtained from an edible non-GM biological source (rooster combs from *Gallus gallus*). The source organism is fully characterized and this and/or the food obtained from it are not detrimental to human health according to the applicant. Rooster combs have a long established history of human consumption in Europe and continue to be part of the normal diet in some countries, including frequently consumed dishes such as home-made recipes (stews) and industrially prepared soup concentrates. They are considered a delicacy in restaurants in countries such as France and Spain. The applicant states that first evidence of the use of rooster combs is found in medieval recipe books from the 15th century. *Gallus gallus* combs used as the source of the novel ingredient are declared as fit for human consumption.

13. Rooster comb is a moderately thin, fleshy formation of smooth soft surface texture, firmly attached from the beak along the top of the skull with a strong base. Rooster comb can measure more than 7 cm in length and weigh more than 8 grams.

Discussion: The Committee did not raise any concerns relating to this section of the dossier.

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

Information on this aspect is provided on p 37-42 of the application dossier

14. RCE is proposed for use in milk-based fermented beverages, yogurts, milks and fromage frais for the general population, with the exception of pregnant women, children and people allergic to sodium hyaluronate and/or avian proteins. These products are intended to be taken in one daily serving containing 80 mg of RCE.

15. The applicant intends that RCE-containing products will be consumed by the adult population, sportsmen, the elderly, and menopausal women. The Secretariat has asked the advice of the Medicines and Healthcare products Regulatory Agency, who advised that sodium hyaluronate from RCE, or from any other source, would not be regarded as medicinal. The applicant is aware that any claims relating to maintaining joint health may be regarded as health claims and require approval under the EU Nutrition and Health Claims Regulation (Regulation (EC) No 1924/2006).

16. RCE's components are present in a comb at an approximate proportion of 1%. The applicant states that 25 g of rooster combs (considering a meal portion of 3 combs of approximately 8 g per comb) contain 250 mg of the components found in the extract. The recommended daily dose (80 mg) is therefore equivalent to consumption of a single comb.

17. In order to calculate the maximum estimated consumption of the RCE, it has been assumed that all dairy products consumed daily would contain the extract. Predicted total dairy intake for

European countries has been obtained from the FAOSTAT (Food and Agriculture Organization of the United Nations) database.

18. In countries with the highest total dairy intake, namely Finland (975.34 g/capita day) or Sweden (1032.88 g/capita/day), the inclusion of RCE in all dairy products would result in an intake of 0.624 g/capita/day of RCE for Finland and 0.661 g/capita/day for Sweden.

***Discussion**: Members requested that the applicant provides a more complete set of intakes data taking into account non-target groups such as children. The applicant stated that it intends to label foods containing RCE to reduce the likelihood of consumption by non-target groups such as children and pregnant women. The applicant acknowledged that it is nevertheless possible that children may consume RCE-containing foods e.g. fromage frais on occasions. The applicant therefore calculated an estimated daily intake of RCE on the basis of mean consumption of dairy products by schoolchildren (aged 4-10) and toddlers (aged 12m). Even in the worst case scenario estimation (i.e. assuming that all dairy desserts would contain RCE, which is not a likely scenario), the estimated daily intake of RCE would be less than 2.4 mg/kg bodyweight/day for children and 3.8 mg/kg bw/day for toddlers. The Committee also considered estimates based on high level consumption of yoghurt and fromage frais by toddlers, provided by the Food Standards Agency using data from the British National Diet and Nutrition Survey. This analysis showed that the intake of RCE could be up to 9.3 mg/kg bodyweight/day.*

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

Information on this aspect is provided on p 43-46 of the application dossier

19. The applicant notes that rooster combs have been consumed in the EU. Also, there are several food supplements on the EU market (Belgium, France, Germany, Ireland, Italy, Portugal, Spain, and UK), containing sodium hyaluronate. According to the applicant, these supplements do not specify the source of sodium hyaluronate except one which is obtained by microbial fermentation, and no adverse effects have been reported.

***Discussion:** The Committee did not raise any concerns about this section of the dossier.*

XI. Nutritional information on the novel food

Information on this aspect is provided on p 47-49 of the application dossier

20. The applicant states that RCE in dairy products is not intended to replace any existing food ingredient. The applicant provided nutritional information for skimmed yogurt, for RCE and for RCE-supplemented skimmed yogurt. The quantity of RCE added to the yogurt is very low (80 mg per portion) and will not have any nutritional impact on a balanced diet. The only nutritional parameter of the yoghurt which is increased by adding RCE is sodium (3% increase relative to non-supplemented yogurt), but the supplemented yogurt remains a “low sodium” food (72.25 mg per 125 g of yogurt).

***Discussion:** The Committee did not raise any concerns about this section of the dossier.*

XII. Microbiological information on the novel food

Information on this aspect is provided on p. 50 of the application dossier

21. The applicant has provided microbiological specifications and has also supplied results of analyses for ten independent lots of RCE. All batches comply with the specifications.

22. The applicant states that RCE is manufactured using Good Manufacturing Practice and is obtained from animals declared fit for human consumption. The applicant has also provided a viral safety report. Stability studies conducted on RCE-supplemented yoghurt indicate that addition of RCE to yoghurt does not promote the presence of pathogenic organisms.

***Discussion**: The applicant confirmed to the Committee that all tests for potential pathogenic micro-organisms indicated that the relevant species were absent and the Committee was satisfied that the microbial composition of yoghurt was not significantly changed by the addition of the novel ingredient.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on p. 51-87 of the application dossier

23. The applicant has conducted a range of toxicity studies which are summarised below. The applicant concludes that these studies demonstrate that the extract is safe and rule out any toxicological concerns relating to RCE. The No Observed Adverse Effect Level (NOAEL) established from these toxicity studies is 600 mg/kg/day, which is the highest dose used in the feeding studies. For a 60 kg adult, this would equate to approx. 5.76 g/capita/day of RCE, according to the dose extrapolation method of Reagan Shaw *et al*., 2007.

24. In their application dossier (section IX.3) the applicant estimated the "worst-case" intake of RCE in different EU member states, based on the extreme assumption that RCE is added to all dairy products, and showed that the resulting intakes would be between 4.5% (for Bulgarian consumers, 0.263 g RCE/day) and 11.4% (for Swedish consumers, 0.661 g RCE/day) of the human equivalent of the NOAEL.

Study Title	Type	Subject studied	Route of Admin-istation	Dose	Safety conclusions drawn by applicant
Genotoxicity study	In vitro	Salmonella, E.coli	-	5 concen-trations	No toxicity in any of the strains, no mutagenic responses

Study Title	Type	Subject studied	Route of Admin-istation	Dose	Safety conclusions drawn by applicant
Acute oral toxicity study in rats	In vivo	18 rats	Oral (gastric gavage)	1000mg/kg, 2000mg/kg	No mortality at 2000 mg/kg, No clinical signs during or after treatment.
2 week dose range finding study	In vivo	40 rats	Oral (gastric gavage)	200, 400, 600 mg/kg/day	No mortality neither alterations in feed consumption, body weight or necropsies, no clinical signs observed
Oral toxicity by 4 weeks repetitive administration	In vivo	100 rats	Oral (gastric gavage)	5, 55, 600 mg/kg/day	No mortality neither alterations in feed consumptions, body weight or necropsies. No clinical or histological signs observed.
13-week oral (gavage) toxicity in rats with a 4-week recovery period	In vivo	100 rats	Oral (gastric gavage)	5, 55, 600 mg/kg/day	No mortality neither alterations in feed consumption, body weight or necropsies No clinical or histological signs observed.
Acute intraperitoneal toxicity in rat	In vivo	26 rats	Intra-peritoneal	250, 500, 900, 1000 mg/Kg/day	No mortality observed. Observed clinical signs post administration as abnormal locomotion, piloerection. Minimum Lethal Dose of the RCE established is more than 1000 mg/Kg

Study Title	Type	Subject studied	Route of Admin-istation	Dose	Safety conclusions drawn by applicant
Study of the intestinal absorption of RCE	In vitro	6 rats	-	Solution of 200 µg/ml	The RCE is absorbed from the media through the intestinal mucous. The most important absorption occurs in the duodenum
Study of the effects of the RCE on Hyaluronic Acid concentration in a horse model. (60 days administration)	In vivo	12 horses	Oral	250 mg/day	No adverse events related to the study products were observed. No significant changes were observed in plasma and synovial fluid analyses. Treated horses presented higher levels of hyaluronate in the synovial fluid.
Clinical trial on efficacy and safety of RCE (8 weeks administration)	In vivo	20 adults	Oral	80 mg/day	No serious adverse events were reported. The RCE appeared to be well tolerated and safe. No alterations in body weight, vital signs, and safety laboratory results.
Clinical trial evaluating the efficacy and safety of a yoghurt supp-lemented with RCE.	In vivo	40 adults	Oral	80 mg/day	No significant changes in body weight or clinical parameters as pulse rate or blood pressure were observed.

***Discussion**: Members questioned the use of the Reagan Shaw et al. method by the applicant and viewed the use of this method as rather unusual in the context of food-related exposure assessments. Members requested an explanation for using this method rather than conventional safety factors. The applicant explained that the method described by Reagan Shaw et al. provides a means of converting the dose of a substance used in animal studies into the Human Equivalent Dose (HED) using inter-species factors based on body surface area. This body surface area*

approach is recommended in US FDA guidance for industry when estimating the safe starting dose for clinical trials (after the incorporation of a suitable safety factor).

The NOAEL for RCE, based on animal feeding studies, is 600 mg/kg bodyweight/day. The applicant calculated that the human equivalent dose is 5.76 g/capita/day for an adult weighing 60 kg, (i.e. 96 mg/kg bodyweight/day). This calculation does not include a safety factor.

Although the applicant did not specifically argue against the conventional "ADI" approach, which is generally used for substances in food, they argue that a 100-fold safety factor would be excessive in light of the properties of hyaluronic acid, the main component of RCE.

Using a conventional food safety approach, and without making the adjustment for body surface area, the Food Standards Agency calculated that the applicant's "worst case" intake assessments provide a safety factor of between 54 (for Swedish consumers, 0.661 g RCE/day) and 137 (for Bulgarian consumers, 0.263 g RCE/day) when compared with the NOAEL from the animal feeding studies, assuming an adult body weight of 60kg.

Members were satisfied that there were no outstanding questions relating to this section of the dossier. While it was possible that the safety margin between intake of RCE by toddlers and the NOAEL from animal feeding studies would be less than 100, this intake represented a worst case scenario involving a combination of assumptions that was extremely unlikely to occur in practice. The Committee therefore concluded that there was no significant concern relating to consumption by children, but advised that any future request for a wider range of uses of this ingredient should be accompanied by a better assessment of intake.

XIV. Allergenicity and labelling

Information on this aspect is provided on p.38 and p. 44 of the application dossier

25. The applicant stated in the dossier that no allergic episodes have been described in the human and animal studies as a result of RCE supplementation. RCE contains sodium hyaluronate (60-80%), glycosaminoglycans (about 20%) and partially hydrolyzed proteins (about 20%). Both sodium hyaluronate and glycosaminoglycans according to the applicant have a broad history of use in the EU market (as oral food supplements) without any documented adverse reports related to allergenicity. The proteins present in the RCE are partially hydrolyzed, with a mean molecular weight of 1234 ± 5 Da, and for this reason the applicant states that their allergenic potential is very low.

26. The applicant acknowledges that in theory there could be some cases of hypersensitivity to sodium hyaluronate or avian proteins. Thus, the applicant proposed to include a warning label for RCE-containing foods for people allergic to sodium hyaluronate and/or avian proteins to illustrate that RCE-containing foods are unsuitable for such individuals.

***Discussion**: The Committee stated that, in the absence of evidence that components of RCE posed a risk, the applicant's proposal to label foods containing RCE as unsuitable for those with allergies*

to avian proteins was too restrictive and will limit consumer choice, perhaps unnecessarily. The applicant therefore agreed to determine experimentally whether the hydrolysed proteins in RCE have the ability to cross-react with egg proteins that are known to elicit allergic reactions. This was done using indirect inhibition ELISA to investigate the ability of RCE to bind serum IgE from egg allergic patients.

The applicant reported that none of the three batches of RCE tested showed any capacity to bind to IgE from pooled sera of patients with egg allergy. The applicant also highlighted the relatively small size of the hydrolysed proteins in RCE and the fact that RCE is derived from connective tissue (mainly collagen) which is known to be less allergenic than egg. The Committee concluded that these additional data were of high quality and provided adequate reassurance that the proteins in RCE were unable to cross-react with egg proteins. The Committee also considered the remote possibility that individuals allergic to chicken meat may be allergic to the proteins in RCE and advised that RCE-containing foods be labelled to reflect this.

Although not a safety-related issue, Members were interested in more detail about the source of the sera used in the ELISA and whether these samples were obtained with ethical consent. The applicant confirmed that the sera were sourced in an ethical way and provided documentation to support this. The study centre CIAL (the Institute of Food Science Research of the Spanish National Research Council) was also granted authorisation from the corresponding bioethics committee. The Committee was satisfied with the applicant's responses.

Although no further information was requested from the applicant relating to labelling, the Committee highlighted the need for suitable labelling of RCE-containing foods to alert non-target groups and vegetarians to the presence of the novel ingredient. As it is a product of animal origin, the source of RCE needs to be clearly stated, especially if it is used in foods that are otherwise regarded as suitable for vegetarians, such as dairy products.

CONCLUSION

The ACNFP has completed its assessment of RCE as a novel ingredient to be added to a range of foods and did not have any significant safety concerns relating to this ingredient.

During its assessment of RCE, the Committee requested further information from the applicant on the following:

- Allergenicity
- Toxicology
- Intakes

- Microbiological information
- Animal welfare issues

After reviewing the applicant's responses to these issues, the Committee did not have any outstanding safety concerns.

The Committee has also reviewed public comments relating to the dossier that were received during a public consultation and has considered these as part of its assessment.

The Committee's assessment focuses on safety and labelling and does not address any nutrition or health benefits that may be claimed for the novel ingredient or for foods that contain it. Nutrition or health claims may only be made if they are specifically authorised under EU Regulation (EC) No 1924/2006. In the case of Rooster Comb Extract, which is proposed as a dietary source of hyaluronic acid, the Committee notes that this substance is produced endogenously in the human body, and that EFSA has advised that a cause and effect relationship has not been established between the consumption of hyaluronic acid and the maintenance of normal joints[19];

The Committee therefore concluded that RCE, added to milk-based fermented beverages, yogurts, milks and fromage frais at the levels proposed by the applicant, is unlikely to present a health risk to consumers. The Committee emphasised that, if the novel ingredient is authorised in the EU, foods into which it is incorporated should be clearly labelled so as not to mislead consumers. Particular care should be taken to inform consumers of the source of the ingredient if it is added to products that are otherwise regarded as suitable for vegetarians.

October 2011

[19] EFSA Journal 2009; 7(9):1266 http://www.efsa.europa.eu/fr/efsajournal/pub/1266.htm

(e) **OPINION ON AN APPLICATION UNDER THE NOVEL FOOD REGULATION FOR A DHA AND EPA RICH OIL FROM THE MICROALGAE SCHIZOCHYTRIUM**

Applicant	**Martek Biosciences**
Responsible Person	**Rodney Gray**
EC Classification	**2.2**

1. An application has been submitted by Martek Biosciences for the use of a Docosahexaenoic acid (22:6(n-3), DHA) and Eicosapentaenoic acid (20:5(n-3), EPA) rich algal oil as a novel food ingredient.

2. This is the third application made by Martek for an oil rich in polyunsaturated fatty acids obtained from the microalgae *Schizochytrium sp.* This oil differs from the one described in the previous applications[20] in that it contains significant quantities of EPA as well as DHA, more closely resembling the composition of fish oil. The applicant proposes that the oil should be used in a similar range of foods to those that are permitted for the original oil. The minor amendments to the proposed level of use in certain products are a reflection of the amounts that would be needed to support a health claim linked to the consumption of polyunsaturated fatty acids (PUFAs); in line with recent opinions from the European Food Safety Authority (EFSA).

3. For the purposes of this opinion the novel ingredient will be referred to as **DHA-O**, which is the name used in the application dossier. Reference to **DHA-S** (both here and in the dossier) applies to the company's DHA rich algal oil which has previously been authorised.

I Specification of the Novel Ingredient (NI)

Dossier pp 6-14

4. The applicant has provided a specification for DHA-O that is consistent with the approved specification for DHA-S, apart from a lower level of DHA (not less than 22.5%, instead of not less than 32%), and a minimum level of 10% for EPA This specification is detailed below and in Tables 3 and 4 of the dossier, which also sets out the analytical results for three batches of DHA-S, each being within specification. In each case the measurable level of DHA is significantly higher than 22.5% and the applicant has advised that this is to allow for standardisation of the algal oil with vegetable oil (see Section XI).

[20] Commission Decision of 5 June 2003 authorising the placing on the market of oil rich in DHA (docosahexaenoic acid) from the microalgae *Schizochytrium sp.* as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (2003/427/EC);
Commission Decision of 22 October 2009 concerning the extension of uses of algal oil from the micro-algae *Schizochytrium sp*. as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (2009/778/EC)

Proposed Specification of DHA-O	
Test	**Specification**
Acid value	Not more than 0.5 mg KOH/g
Peroxide value (PV)	Not more than 5.0 meq/kg oil
Moisture and volatiles	Not more than 0.05%
Unsaponifiables	Not more than 4.5%
Trans-fatty acids	Not more than 1%
DHA content	Not less than 22.5%
EPA content	Not less than 10%

5. DHA-O contains a range of fatty acids, of which DHA and EPA, together with palmitic acid, are the most abundant (Dossier, Table 7). The applicant also provides details of the unsaponifiable component (Dossier, Table 8) noting that the sterols present in the product are commonly found in the diet.

6. The applicant also provides results of analyses of heavy metals, protein and residual solvents, which are consistent with those seen for DHA-S (Dossier, Table 5). Levels of polycyclic aromatic hydrocarbons, dioxins, acrylamide and pesticide residues have also been examined and all were found to comply with published limits (see Dossier, Tables 9, 10, 11, pp 12-14).

Discussion *The Committee was satisfied that the composition of DHA-O did not give rise to any safety concerns.*

II Effect of the production process applied to the NI

Dossier pp15-21

7. The production process used to produce DHA-O is very similar to that used for the production of DHA-S. The process involves the fermentation of algae from the genus *Schizochytrium sp* in a pure culture, heterotrophic fed-batch fermentation process followed by an oil recovery stage.

8. Once sufficient cell mass is available the oil recovery stage begins, involving either fresh broth or reconstituted dried algae. The broth is first treated with antioxidants, followed by heating and pH adjustment, prior to homogenisation to induce cell lysis and to release the oil. The resulting broth is cooled and isopropyl alcohol is added to form an emulsion. The applicant then separates the oil from the aqueous phase by centrifugation. The oil phase is dried and then refined using

methods commonly used by the vegetable oil industry to obtain clear oil. The oil recovery process is significantly different from the one used for DHA-S, which relied on solvent (hexane) extraction of oil from the dried biomass prior to refining.

Discussion *The Committee noted that the production process was similar to that used for the production of DHA-S and, although the differences in the extraction procedure were noted, Members were content that they did not give cause for concern.*

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

Dossier, pp

9. The alga used in the production of DHA-O is a previously unpublished member of the genus *Schizochytrium* which was selected by the applicant following a strain selection process. The production strain has not been genetically modified. The strain was selected for its ability to produce EPA and further improvements in productivity were obtained by optimisation of the fermentation process.

10. The applicant provides a detailed overview of algal toxin production noting that, based on both published and unpublished studies, there have been no reports of toxic compounds, or association with toxic compounds, produced by Thraustochytrids (the order to which *Schizochytrium* belongs). The company also notes that most of the toxic compounds produced by microalgae are produced by blue-green algae or dinoflagellates, which lie in a separate kingdom to *Schizochytrium.* Two toxic compounds, domoic acid and prymnesin, are known to be produced in the Chromista, the Kingdom to which *Schizochytrium* sp. belongs. However, these toxins are largely restricted to two genera (*Pseudonitzschia* and *Prymnesium*) which are in a separate class (Prymnesiophyceae*)*) and phylum, respectively, from the Thraustochytrids. Additional tests carried out by the applicant confirm that neither domoic acid nor prymnesin are present in *Schizochytrium* sp. (Dossier, Appendix 3a).

Discussion *The Committee accepted that Schizochytrium sp had previously been used to produce DHA rich oils and although DHA-O was produced from a newly characterised member of the genus, as there were no reports of toxins being produced by any members of the Class which includes the genus Schizochytrium, the use of the organism as a source of the oil did not give cause for concern. The Committee also accepted that the test results confirming the absence of domoic acid and prymnesin offered additional reassurance in this regard.*

IX Anticipated intake and extent of use of the NI

Dossier, pp

11. DHA-S is currently permitted in a range of food categories and the applicant proposes a similar list of uses for DHA-O. However, the applicant proposes certain changes in order that they, like fish oil producers, can provide products that supply the recommended daily intakes of PUFAs. The applicant notes that these amendments are relatively minor and in line with a recent EFSA

opinion regarding the reference intake values for n-3 and n-6 PUFAs[21]. This opinion concludes that there is evidence of a relationship between intake of PUFAs (EPA, DHA) and cardiovascular health at 250mg per day and this claim is now permitted under the relevant health claims legislation.

12. In addition, the applicant also proposes a high dose supplement (450mg/day) for pregnant and lactating women, referring to recommendations from a number of Government bodies and expert groups (including the EFSA report at Annex B) that pregnant and nursing women should consume at least 450 mg EPA and DHA per day (200mg DHA) in order to compensate for increased metabolic demands associated with pregnancy and lactation. This recommendation takes account of accumulation in the foetus or infant and the requirements for cardiovascular health.

Food use	**DHA-S (Max level of DHA)[1]**	**DHA-O (Max level of DHA+EPA)**
Dairy Products except milk based drinks	200mg/100g; 600mg/100g for cheese	Unchanged
Dairy Analogues except drinks	200mg/100g; 600mg/100g for cheese analogues	Unchanged
Spreadable Fats and Dressings	600mg/100g	Unchanged
Breakfast Cereals	500mg/100g	Unchanged
Foods for Particular Nutritional Uses as defined in Commission Directive 2009/39/EC, but excluding infant and follow on formula	In accordance with the nutritional requirements of the persons for whom the products are intended	Unchanged
Foods Intended for use in energy restricted diets for weight reduction	200mg/meal replacement	250mg/day
Bakery Products, Breads and rolls	200mg/100g	Unchanged
Nutrition Bars	500mg/100g	Unchanged

[21] http://www.efsa.europa.eu/en/efsajournal/pub/1461.htm

Non-alcoholic beverages	60mg/100g	80mg/100g
Milk Based Drinks	60mg/100g	80mg/100g
Food Supplements	200mg/daily dose	250mg/day
Food Supplements for pregnant and lactating women	-	450mg/day (NEW)

[1] As listed in Commission Decisions 2003/427/EC and 2009/778/EC

Estimated intake

13. The applicant has calculated the mean and 97.5th percentile "all user" intakes for each of the authorised and proposed food categories. This methodology assumes highest possible consumption as it is assumed that all products within a category contain the maximum level of the NI. (The "all user" description indicates that the distribution of intakes is obtained by considering only those individuals who consume the relevant foods, discounting individuals who do not consume them).

14. The results of this analysis indicate that male teenagers potentially have the greatest 97.5th percentile all-user intake of DHA+EPA at 1.72g per day. By body weight, the highest consumers are children (97.5th percentile all-user intake at 62mg) (See table below). These estimates are broadly similar to those seen for DHA-O in which greatest 97.5th percentile all-user intake was for male adults with a consumption of 1.66g/day and, by kilogram body weight children (57mg).

Summary of the Estimated Daily Intake of DHA-O (as DHA+EPA) from all Proposed Food Categories in the U.K. by Population Group – based on NDNS Data

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (g)	Percentile (g)			Mean (g)	Percentile (g)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.8	1,628	0.42	0.67	0.77	0.89	0.42	0.66	0.77	0.89
Young People	4-10	99.6	834	0.65	0.99	1.13	1.23	0.65	0.99	1.13	1.23
Female Teenager	11-18	97.8	436	0.67	1.05	1.20	1.31	0.67	1.05	1.17	1.30
Male Teenager	11-18	99.5	414	0.88	1.33	1.51	1.68	0.88	1.33	1.50	1.72
Female Adult	16-64	94.1	901	0.6	0.95	1.10	1.21	0.60	0.96	1.12	1.23
Male Adult	16-64	94.8	726	0.76	1.23	1.45	1.66	0.77	1.23	1.45	1.65

Summary of the Estimated Daily Intake of DHA-O (as DHA+EPA) from All Proposed Food Categories in the U.K. by Population Group – based on NDNS Data

Population Group	Age Group (Years)	% User	Actual # of Total Users	All-Person Consumption				All-Users Consumption			
				Mean (mg/kg bw)	Percentile (mg/kg bw)			Mean (mg/kg)	Percentile (mg/kg bw)		
					90	95	97.5		90	95	97.5
Children	1½ -4½	98.8	1,628	29	47	54	62	30	48	54	62
Young People	4-10	99.6	834	25	39	44	49	25	39	44	49

Female Teenager	11-18	97.3	436	13	21	24	26	13	21	24	26
Male Teenager	11-18	99.3	414	16	26	28	32	16	26	28	32
Female Adult	16-64	91.6	901	8	14	16	19	9	14	16	19
Male Adult	16-64	91.4	726	9	15	17	20	9	16	18	20

15. **Food Supplements.** The applicant proposes to increase the level of PUFAs from 200mg to 250mg per day and to market a separate 450mg supplement specifically for pregnant and nursing mothers. The applicant is of the view that, as supplements are consumed as an alternative to fortified food products, these products will not significantly affect levels of intake. The applicant also notes that fish oil supplemented products are widely available, and DHA-O is a direct replacement for these products.

Discussion *The Committee was content that the minor changes to the use levels would not lead to an increase in the level of consumption amongst the general population. Members noted the high dose supplements which are targeted at pregnant and nursing mothers were also in line with a recent health claim request that had recently been evaluated by EFSA and noted that this may lead to an increase in gestation periods (See Discussion Section XIII).*

XI Nutritional information on the Novel Food

Dossier p43-

16. The applicant again refers to the rationale for the changes in use categories (see above) and also refers to a 2009 novel food authorisation for a DHA+EPA rich oil from Antarctic Krill (*Euphasia superba),* which has use categories that are consistent with those that have been approved for DHA-S. The applicant also compares the profile of DHA-O with a range of oils including both krill oil, salmon and cod liver oil (Dossier Table 12). Blending with vegetable oils (see Section I above) will enable DHO-O to be formulated in such a way that it closely resembles the composition of existing fish oils, so that it can be used as a direct substitute in manufacturers' recipes.

17. In the previous application the applicant noted that the DHA-S oil is to be added into a range of existing foods, either as a partial replacement for the fat component of the food or as a direct replacement for fish oil (added as an ingredient). The applicant therefore did not envisage that the addition of DHA-S would change the nutritional profile of the food as consumed and they illustrated this by comparing a milk based drink fortified with the NI and with fish oil. Although this information was not repeated in this application, the same reasoning would apply to DHA-O.

Discussion *The Committee accepted that the nutritional information provided was appropriate and the non-fat nutritional profile of a product containing the novel ingredient would not be significantly different when compared with an equivalent product fortified with fish oil. The Committee also noted that the fatty acid profile of the product was broadly comparable with existing fish oil derived products and, as such, would be unlikely to give rise to safety concerns. The Committee also noted that the applicant does not discuss the nutritional profile of the product in terms of its composition as a fat but, as it is almost entirely composed of triglycerides, a caloric value of 9 kcal will therefore be used on nutritional labels, as is currently used for DHA-S.*

XII Microbiological Information

Dossier p46

18. The applicant notes that DHA-O is a lipid with little water activity and would not support the growth of microorganisms. The company may elect to pasteurise the cell biomass and the solvent recovery stage also requires the application of heat and would kill any vegetative cells present. The applicant has included a specification for the presence of microorganisms (Dossier, p46, Table 19) and also shows the results for three individual batches of the oil, each of which were within the specification.

Discussion *The Committee accepted the data provided in the application although Members regarded the possibility of contamination by Cyanobacteria to be one that should not be discounted. In regard to this point, Members were reassured by the quality control regime and confirmation from the applicant that that the fermentation proceeds in the absence of light under axenic*[22] *conditions. The Committee accepted that these measures were sufficient to ensure that any risk of Cyanobacterial contamination was no greater than for any other closed system fermentation process used in food production.*

XIII Toxicological information

Dossier p.72-77

19. In addition to the toxicological studies carried out on DHA-O (see below), the applicant notes that its traditional counterpart, fish oil, is widely used both in food supplements and in fortified foods in the EU without restriction. The applicant also highlights the absence of algal toxins and the broad similarity between DHA-O and DHA-S, meaning that the toxicological studies carried out in support of the earlier product have some relevance to DHA-O. These data are not supplied again in the current application, but are summarised in the Committee's 2002 initial opinion on DHA-S[23].

20. **14 day dose ranging study**. This study, carried out according to OECD guidelines, indicated that doses up to 60,000 mg/kg/day should be administered to rodents in the 90-day repeat dose toxicity study. Food efficiency changes were viewed to be non-adverse and toxicologically insignificant. A single reported death was viewed to be as a result of anaesthesia.

[22] axenic: a pure culture of a single organism.
[23] http://www.acnfp.food.gov.uk/assess/fullapplics/60694

21. **90 day toxicity study.** Carried out in accordance with relevant OECD guidelines. DHA-O (0 – 5% in the diet) was administered to Sprague-Dawley rats for the duration of the study with a fish oil being used as a control. Although a number of statistically significant changes were observed *e.g*. body weight gain, food consumption and food efficiency, these were attributed to high dietary fat concentrations, in general, and not specifically to DHA-O. The administration of DHA-O at levels of 0.5%, 1.5% and 5% resulted in a dose-dependent increase in DHA levels in plasma, liver, and brain. DHA levels were generally higher in females than males. With a few exceptions, and in all groups, EPA plasma and liver concentrations were generally lower compared to DHA concentrations, and were generally higher in females. Plasma EPA concentrations were higher than those seen in the liver.

22. There were no adverse changes in haematology, clinical chemistry, coagulation, or urinalysis parameters in male or female rats that were attributable to the administration of DHA-O. Statistically significant findings in red cell mass and clinical chemistry were seen but these were of small magnitude and, as similar effects have been historically observed with high fat diet diets, they were considered to be non-adverse and toxicologically insignificant. There were no macro- or micro-scopic findings related to administration of DHA-O. Incidental histological findings included masses involving the penis that corresponded to abscesses or duct ectasia involving the preputial glands, unilateral masses of the epididymides that corresponded to sperm granulomas, hepatodiaphagmatic nodule and fluid-filled uteri/fallopian tubes.

23. An increased incidence of alveolar histiocytosis in the lungs of males and females in two groups was related to the unintended aspiration of the test substance (fish oil or DHA-O) into the lungs, in association with aspiration of food meal. A single, benign mammary gland fibroadenoma in one high-dose female was most likely a spontaneous neoplasm, not associated with the administration of the test substance. In general, the absolute and relative liver (males and females) and kidney (females) weights were significantly increased. However, these values were significantly lower than in the fish oil control group.

24. Incidental findings included absolute adrenal (female) and testicular (male) weight changes which were not attributable to DHA-O. Changes in kidney weight were considered incidental without notable clinical chemistry changes, while increases in liver weight (males and females) are considered secondary to high fat diet intake, as similar effects were observed with fish oil.

25. The applicant has concluded that there was no toxicity related to administration of DHA-O in male or female rats. Under the conditions of this study and based on the toxicological endpoints evaluated, the no-observed-adverse-effect level (NOAEL) for DHA-O in the diet was judged to be 5% (50,000 mg/kg) for male and female rats, equivalent to 3149 and 3343 mg/kg body weight/day, for male and female rats respectively.

26. **Genotoxicity studies.** The applicant viewed the results of a reverse mutation (Ames) assay, carried out to OECD Guidelines, to indicate that DHA-O was non-mutagenic. An *in vitro* mammalian chromosome aberration test and an *in vitro* mouse micronucleus test did not report any unusual findings.

27. The applicant concludes that these studies demonstrate that the intake of DHA-O arising from consumption in the proposed food categories does not give rise to any safety concerns noting that their NOAEL value equates to consumption of approximately 200g of DHA-O per day for a 60kg adult.

28. The Committee asked that the applicant provide reassurance that its proposal to target a high dose supplement at pregnant and nursing women was supported by available safety data, noting that there have been reports of increased gestation in women who consumed a high fish oil diet. The applicant's response noted that a meta-analysis of trials involving the supplementation of up to 3g n-3 PUFAs in women with high risk pregnancies reported a reduced risk of pre-term delivery, while other trials report decreased maternal adverse events during labour and delivery together with decreased infant morbidity. Although the applicant acknowledged that a consequence of extended gestation could be an increase in post-term births, in their view, this does not appear to be borne out by an analysis of the available data which do not appear to identify an increase in post-term births compared with the reported national averages.

Discussion

The Committee concluded that the range of the toxicological studies carried out by the applicant were sufficient to assure the safety of the product at the proposed levels of use. Members noted that concerns related to post-date births had not been addressed by the applicant's response. Members disagreed with the applicant's conclusions regarding reviews by Makrides at al. in 2006[24] and 2010[25], noting that the latter paper provided evidence that there is a valid concern in relation to post-date births and high intakes of n-3 fats. However the Committee accepted that any increase in gestation periods was a generic issue that had previously been taken into account both by EFSA and the UK Scientific Advisory Committee on Nutrition when setting recommended intake levels for long chain polyunsaturated fatty acids in pregnant and lactating women, but suggested that possible effects of increased gestation should be taken into account when considering the levels at which the novel ingredient is used, and when monitoring possible adverse events following its widespread introduction into the diet.

Allergenicity and Labelling

29. The level of residual protein in DHA-O is less than 0.02%, measured by the Kjeldahl method (Dossier Table 5). The applicant notes that DHA-S is produced from very similar source materials and also contains low levels of protein (<0.1%), and has not been associated with any serious adverse events. The applicant also notes that reports of respiratory and dermatologic responses (including allergy) to microalgae have been restricted to human exposure to blue-green algae.

30. The applicant does not make any proposal for the labelling of this ingredient. The authorisation for the existing product DHA-S requires it to be labelled as "DHA-rich oil from the microalga *Schizochytrium sp".*

[24] Makrides M, et al., 2006. Database of Systematic Reviews. Issue 3, Article No. CD003402
[25] Makrides M, et al. 2010. JAMA 304:1675-1683.

Discussion *The Committee agreed that DHA-O was not an allergenic risk and that labelling similar to that of DHA-S adequately describes the product.*

Overall Discussion

The Committee concluded that the applicant had provided sufficient scientific data to assure them that the proposed additional uses of the DHA-O did not give rise to specific concerns over safety when consumed at the proposed levels of use. The Committee highlighted that current policy in the UK is to encourage the intake of long chain n-3 polyunsaturated fatty acids and that this product may help consumers with low intakes to increase their consumption of n-3 fatty acids[26]*.*

Concerns have been raised during the previous assessments of novel PUFA-rich algal oils about the impact that long term, high-level consumption of these products may have on health. Members noted that this should be kept under review and intakes of DHA should monitored at national and/or EU level. However, the Committee reiterated their view that this uncertainty was not solely related to the extension of use of this DHA and EPA rich oil "DHA-O" and any studies that looked at the impact of consumption of foods fortified with n-3 long chain polyunsaturated fatty acids should address all dietary sources and different age groups, particularly children.

Conclusion

The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by the applicant, Martek Biocsciences that the range of uses for the novel ingredient (DHA and EPA rich algal oil from *Schizochytrium* sp., DHA-O) is acceptable.

December 2011

[26] Advice on fish consumption: Benefits and Risks; SACN/COT 2004

(f) Polyvinyl Methyl Ether Maleic Anhydride Co-polymer

Andreas Klepsch
European Commission

13 October 2011

Dear Mr Klepsch

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.

The ACNFP was generally in agreement with the conclusions of the Dutch initial opinion but expressed some concern relating to the potential effects of this co-polymer on human gut flora. This concern stems from research papers presented by the applicant showing that use of the copolymer in dental products has a significant effect on bacterial growth in the mouth. However, its effect on bacteria in other parts of the gut has not been investigated and the ACNFP requested that the applicant provide clarification on this potential effect.

The UK therefore cannot support the authorisation of this ingredient until the applicant has provided suitable reassurance about its effects on gut flora.

The ACNFP also discussed the following issues, which may be of interest:

- The Committee was in agreement with the Dutch CA's emphasis on detailed specifications relating to any contaminants that may be present in preparations of the novel ingredient. The Committee stressed that it is extremely important that applicants routinely use appropriate, validated methods capable of detecting and quantifying relevant contaminants that may be present in novel ingredients and that details of all these methods are clearly described.

- The Committee discussed intakes and potential toxicological effects in children but was ultimately content that a large safety margin still exists which is sufficient to provide reassurance of safety.

Yours sincerely,

Dr Manisha Upadhyay

Novel Foods Unit, Food Standards Agency

(g) Antarctic krill (*Euphausia superba*) – Extension of Use

Andreas Klepsch
European Commission

17 November 2011

Dear Mr Klepsch

As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Finnish CA for the above product.

The ACNFP was generally in agreement with the conclusions of the Finnish initial opinion and the UK does not wish to raise any objections.

The Committee did however raise a question about the possible implications for consumers of consuming a range of foods containing fish or marine oils in relation to overall intakes of dioxins, heavy metals and other contaminants; and particularly any implications this may have for vulnerable groups such as pregnant women.

The presence of dioxins and various other contaminants in foods are recognised as a hazard and as such regulated at EU level by setting maximum levels with which relevant foods and food ingredients (including, specifically marine oils) must comply by law, thus minimising the opportunity for consumers to exceed tolerable levels for these contaminants. Therefore, although the UK notes a trend towards increasing consumption of marine oils, on balance these measures afford sufficient protection to ensure consumer safety.

Yours sincerely,

Dr Manisha Upadhyay

Novel Foods Unit, Food Standards Agency

(h) Coriander seed oil (*Coriandrum sativum L*)

Andreas Klepsch
European Commission

1 December 2011

Dear Mr Klepsch

As the UK Competent Authority (CA), the Food Standards Agency has sought advice from the Advisory Committee on Novel Foods and Processes (ACNFP) on the initial assessment report prepared by the Irish CA for the above product.

Based on the ACNFP's advice, the UK is unable to support the favourable Irish opinion and wishes to raise objections to the authorisation of this novel ingredient without the provision of additional information from the applicant Nestec.

The ACNFP requested clarification from the applicant on two key issues:

- **Metabolism**

The ACNFP advised that the applicant has provided insufficient data on the metabolism of the petroselenic acid constituent of the novel ingredient and its impact on other fatty acid metabolism at doses relevant to intended exposure. In the absence of clinical data, this lack of information results in a level of uncertainty which suggests caution. The proposed use will exceed current average consumption levels of oil from coriander seed by twenty times and the Committee suggested it may be prudent to seek additional data from the applicant.

- **Allergenicity**

The ACNFP did not regard the Kjeldahl method as a satisfactory protein assay to demonstrate lack of allergenic potential of the novel ingredient. The quantification limit (0.1g/100g) is not sufficiently sensitive to provide reassurance of the absence of potential allergens given that coriander is botanically related to celeriac and celery and therefore potentially capable of triggering severe allergic reactions in individuals allergic to proteins within this family of plants (*Umbiliferae*).

The ACNFP's view is in line with that of EFSA who have also rejected the Kjeldahl assay as a method for determining allergenic potential, for example ,
http://www.efsa.europa.eu/fr/scdocs/doc/154.pdf.

The ACNFP therefore requested the applicant to provide additional information to demonstrate lack of allergenic potential of the novel ingredient.

I am happy to prvide any further clarification.

Yours sincerely,
113

Dr Manisha Upadhyay

Novel Foods Unit, Food Standards Agency

(i) Synthetic Vitamin K2

Andreas Klepsch
European Commission

(By email)

27 January 2012 NFU 794

Dear Mr Klepsch

As the UK Competent Authority under regulation (EC) 258/97 on novel foods and novel food ingredients, the Agency has consulted members of the Advisory Committee on Novel Foods and Processes on this application and on the initial assessment report provided by the German Competent Authority (CA). The UK agrees with the positive opinion of the German CA but has the following comment.

We agree with the comments of the German CA in regard to storage conditions and the requirement carry out additional analyses to determine an appropriate shelf life. In particular, we note that a consequence of storage in direct sunlight could be the generation of toxic metabolites. We would therefore request that additional data generated by the applicant in this regard are circulated in advance of any decision to authorise the product.

Yours sincerely

Dr Chris Jones

UK Competent Authority

(j) Gamma Amino Butyric Acid Comments from the UK.

The UK endorses the view of the Irish Competent Authority that an additional assessment is required. In addition, we would like to offer the following comments.

- Gamma amino butyric acid (GABA) comprises less than 1% of the novel ingredient which is poorly characterised in composition but is known to contain about 30% protein. Although GABA is present in other foods there does not appear to be any record of the previous consumption of Lactobacillus-fermented grape must and it would be reasonable to require a more detailed characterisation and toxicity testing of novel ingredient rather than to rely partly on a history of safe use of the two separate components.

- There is evidence for orally administered GABA (in large doses) raising growth hormone levels in humans, and it also has the potential for neurological effects. The argument for its safety appears to be that, based on animal studies; it is not efficiently absorbed from the intestine (despite evidence of a specific GABA transporter in the rat). Certainly there seems to be a lack of adequate information on absorption in humans on which to base an assessment. There is also a question of the relevance of animal data in assessing neurological effects.

- The 13 week rabbit study is poorly designed and cannot be regarded as a substitute for a conventional 90d study in rats. The results highlight a number of issues:

    - Mortality due to mis-dosing resulted in group sizes for control, reference, low and high dose respectively of 5, 5, 4, 4 for males and 5, 5, 5, 3 for females. These numbers are not adequate for a critical study and there could be some question as to why all deaths occurred in the treated groups and not in the control or reference groups.
    - The mortality (if due, as indicated, to mis-dosing) represents poor practice and gives concern about the experience and expertise of the laboratory.
    - Conclusions on group mean values are not likely to be meaningful due to the small group sizes. However both treated groups had reduced food intakes and there are relative organ weight differences in the high-dose group which need further explanation given the statistical weakness of the study.
    - The conversion from g/animal/day into g/kg bw/day is not given. Is it correct to assume that the 2 kg body weight at start of the study meant that the dosing gave a maximum of 6.75 g/kg bw/day of the product at high dose and 3.375 g/kg bw/day at the low dose?
    - This test material does not solely contain GABA thus to represent the dose in terms of GABA is misleading.
- The statements *'the primary purpose of adding this NI to foods it for its putative health benefits as a scavenger of free radicals'* and *'it is intended as a nutritional support for people wishing to counter free radicals"* are both of limited value in the context of a safety assessment, and meaningless to an average consumer.

- The applicant refers to the use of labelling to ensure that vulnerable groups do not consume the product but the rationale for this, and why other vulnerable groups are not identified, is not clear.

Food Standards Agency
September 2011

(k) UK response to the European Food Safety Authority's public consultation concerning draft guidance for the risk assessment of engineered nanomaterials in food and feed.

The UK Food Standards Agency's response was provided on the basis of advice from the Advisory Committee on Novel Foods and Processes (ACNFP), the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), the Committee on Carcinogenicity of Chemicals in Food, Consumer Products and the Environment (COC) and the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM)

General comments

The guidance seems basically sound. A reasonable and pragmatic approach mwhich seems very appropriate and positive. One criticism however is that the guidance may be too prescriptive for an area which is rapidly developing and more flexibility would avoid the guidance becoming outdated quickly. An additional consideration is that at a time where efforts are being made to reduce animal testing, are all the studies listed for the risk assessment of engineered nanomaterials necessary and has EFSA considered an alternative approach to animal testing. For example, an alternative approach may be to distinguish where a new nano product may differ from the non-nanoform and devise an appropriate test.

The document does not mention how risk assessment for foods containing engineered nanomaterials is being approached in the rest of the world e.g. US, Japan although this is part of the terms of reference. This guidance could usefully be set out in the context of naturally occurring nanostructures in food. For example thermal treatments, such as those often used to cook foods, may give rise to nanoscale protein structures and aggregates. A surprising factor was that there was no reference in the opinion to allergenicity, as this is pertinent to consideration of nanoscale materials derived from proteins as there is evidence that the physical form of a protein may affect its digestibility and its allergenic potential.

Characterisation

Table 1 outlining the parameters for characterisation and identification of engineered nanomaterials was very useful.

Genotoxicity

The guidance is fine as it stands but may need revising after further developments with regard to genotoxicity testing, including the conclusions of EFSA's genotoxicity test strategy committee.

As there is limited information on nanoparticles (NP), a larger test baseline would be perhaps advisable. A problem of course, may be the lack of a sufficient spread of reference NPs, known to be genotoxic/carcinogenic and we are not sure how well validated the assays for genotoxicity/carcinogenicity/mutagenicity are against nanoparticles.

***In vivo* testing**

EFSA advises: *In vivo* genotoxicity testing may also be considered where there is evidence for a prolonged inflammatory response from *in vivo* studies. This needs care, since it is not a general genotoxicity testing trigger. Also, conducting a liver unscheduled DNA synthesis test may not be too relevant unless there is liver inflammation. More clarification of the circumstances triggering this type of testing would be helpful, and also which assay and which organ would be studied.

Food Standards Agency

February 2011

(l) Seleniumtriglycerides

Jean Francois Roche
European Commisison

24 May 2011

Dear Jean-Francois,

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 Polish CA for this novel ingredient. We have considered the Polish report and note that this substance requires additional assessment by EFSA before it can be accepted as a new source of selenium in food supplements and in fortified foods, in accordance with the specific legislation in those areas.In reaching a decision on this substance it will be essential to consider the bioavailability of selenium when it is taken in this form, and whether the selenium is taken up in a form that results in altered tissue distribution compared with existing sources. These questions do not seem to be addressed in the initial opinion.

Also, the production process results in hydroxylation of fatty acids and the ACNFP has pointed out that hydroxy fatty acids occur only rarely in the diet. The initial assessment report states that “a small part” of the fatty acids is hydroxylated, but does not consider the extent to which the hydroxy fatty acids are subsequently eserfied, and, whether this poses a risk.

We therefore conclude that this novel ingredient requires further assessment by EFSA, and that the EFSA assessment should take account of the points that are set out above.

Yours sincerely,

(By email only)

Dr Sandy Lawrie

Novel Foods Unit, Chemical Safety Division

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