Application for the Extension of Authorisation of Dihydrocapsiate (DHC) for Food Supplement Use

NON-CONFIDENTIAL

Submitted According to

Regulation (EC) No 258/97 of the European Parliament

and of the Council of 27th January 1997 concerning novel foods and novel food ingredients

AJINOMOTO CO., INC. JAPAN

Mr Takashi Kayahara

Wellness Business R&D Planning Department

15-1, Kyobashi 1-choume,

Chuo-ku,

104-8315,

Tokyo, Japan.

May 2014

Table of Contents

Executive Summary 4
Introduction 5
Requirements 7
1.0 Administrative Data 7
2.0 General Description 8
3.0 Novel Food Categorisation and Requirements 9
I. Specification of Dihydrocapsiate (DHC) 10
II. Effect of the Production Process Applied to the Novel Food Ingredient 13
III. History of the organism used as a source 14
IV-VIII. (Sections not applicable since no GM technology is involved) 15
IX. Anticipated Intake/Extent of use of the Novel Food Ingredient and Supplement 16
IX.1 Authorised Uses and Use-levels of DHC as a novel food ingredient 16
IX.2 Estimated Intakes of DHC as a Novel Food supplement 18
IX.2.1 Potential DHC intakes based on data in original submission 18
IX.2.2 Potential DHC intakes based on 2008-2011 UK food consumption data 19
IX2.2.1 Intakes from food ingredient use 20
IX2.2.2 Intakes from food supplement use 20
IX2.2.3 Total intakes from food ingredient and supplement use 21
IX.3 Is there information to show anticipated intakes for groups predicted to be at risk? 25
IX.4 Will the introduction of the novel food be restricted geographically? 25
IX.5 Will the novel food replace other foods in the diet? 25
IX.6 Food Product Labelling Information 25
IX.7 Conclusion on anticipated DHC Intakes 25
XI Nutritional Information 26
XII Microbiological Information 27
XIII Toxicological and Human Safety Information 28
XIII.1 Is there a Traditional Counterpart? 28
XIII.2 Toxicological and Human Health Assessment of DHC 28
XIII.3 Potential Allergenicity Concerns for Humans 29
XIII.4 Safety Assessment 29

Conclusion 31
Glossary 32
References 33

Tables

Table 1: Authorised uses of DHC as a food ingredient 6
Table 2: Specifications of Dihydrocapsiate taken from Commission Implementing Decision (EC Commission, 2012) 11
Table 3: From EFSA Opinion (2012): Reproducibility of production process 12
Table 4: Authorised uses of DHC as a food ingredient (to provide 3mg per serving) 17
Table 5: Potential intakes of DHC for UK consumers (1992-2001) from authorised use as a food ingredient, per Ajinomoto (2010) Submission to ACNFP and EFSA Opinion (2012) 18
Table 6: Potential intakes of DHC (mg/kg bw/day) resulting from daily supplement consumption giving 3,6 or 9 mg DHC per day by all consumers (1992-2001) 18
Table 7: Maximum total potential intakes of DHC for UK consumers (1992-2001) from use as a food ingredient plus maximum use as a food supplement (9mg). 19
Table 8: Potential intakes of DHC for UK consumers (2008-2011) from authorised use as a food ingredient. 20
Table 9: Potential intakes of DHC resulting from daily supplement consumption giving 3,6 or 9 mg DHC per day by all consumers (2008-2011). 20
Table 10: Proportion of individuals in the UK NDNS Survey 2008-2011 who reported consumption of any non-nutrient food supplement. 21
Table 11: Intakes of DHC resulting from daily supplement consumption giving 3,6 or 9mg DHC per day only by adolescent and adult consumers of non-nutrient supplements (2008-2011). 21
Table 12: Maximum potential intakes of DHC resulting from food ingredient use and daily supplement consumption giving 3,6 or 9 mg DHC per day by all consumers (2008-2011). 22
Table 13: Potential intakes of DHC based on approved food ingredient use levels plus supplementation at 3,6 or 9 mg/day for users of non-nutritional supplements only. 23
Table 14: Intakes of DHC (mg/kg bw/day) resulting from food ingredient use and daily supplement consumption giving 3,6 or 9 mg DHC per day, only by adult consumers of non-nutrient supplements. 24
Table 15: Showing Estimated Ingredient intakes based on use levels providing 3 mg of DHC in an average portion for adults (reproduced from EFSA Opinion, (2012), 30

Appendix 1: Synthetic DHC ‘no objection’ letter in response to an NDI notification of DHC at up to 15 mg a day 35

Executive Summary

In 2010, Ajinomoto Co., Inc. sought approval in Europe under Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27th January 1997 concerning Novel Foods and Novel Food Ingredients, for the use of synthetic Dihydrocapsiate (DHC) as a Novel Food Ingredient (Ajinomoto, 2010).

Authorisation was subsequently granted by the EU Commission on 22 November 2012 for the placing on the market of DHC as a novel food ingredient (EC Commission, 2012).

Dihydrocapsiate belongs to a group of natural substances known as capsinoids which have been shown to occur in a number of chilli and sweet peppers and thus has a long history of consumption. The application requested approval to use synthetic DHC in 5 food categories of interest to food manufacturing companies. Estimates by EFSA showed that when at concentrations delivering 3 mg DHC/portion or serving, concentration levels varied from 8 to 2050 mg per kg resulting in mean daily intakes of round 12 – 13 mg (8.1 mg/day for pre-school children); the 97.5th percentile intakes of adults and the elderly were estimated to be around 34 mg/day (18.5 mg/day for pre-school children). Calculations based on body weights resulted in the highest intakes being for pre-school children (mean: 0.6 mg/kg bw/day; 97.5th percentile: 1.3 mg/kg bw/day).

Extensive evaluation of DHC in genotoxicity and developmental studies found no evidence of toxicity and the no-observed adverse effect level (NOAEL) from three subchronic oral toxicity studies in rats of up to 6 months duration was consistently at 300 mg DHC/kg bw/day. Placebo controlled bolus oral administration human studies with DHC of up to 12 mg DHC/volunteer for 8 days or 9 mg DHC/volunteer for 4 weeks were well tolerated with no evidence of clinically significant findings.

DHC has been determined to be generally regarded as safe (GRAS) as an ingredient at up to 3 mg per serving and more recently as a New Dietary Ingredient (NDI) for supplement use in the United States of America (USA), (Appendix 1.

The EFSA Panel was of the opinion that the margin of safety (MOS) in relation to the NOAEL of 300 mg/kg bw/day is sufficient, including the highest estimated intake of 1.3 mg/kg bw/day for pre-school children and was thus safe under the proposed food ingredient uses and use levels.

Ajinomoto Co., Inc. is now seeking an extension to its current Novel Food Authorisation for food supplement* use at up to 3mg for school children, adolescents, adults and the elderly to be taken up to 3 times a day, ie a maximum daily intake of 9mg/day. Pre-school children have been excluded from this application in accordance with Directive 2002/46/EC (2002) and Part E of Annex II of Regulation (EC) No 1333/2008. There are no changes in the product specification and the production process is the same.

When the estimated intakes were modelled, it became clear that consumption of the food supplement alone by schoolchildren, who have the highest bodyweight related intake, gave a 97.5th percentile intake estimate of only 0.58 mg/kg bw/day which is well below the 1.3mg/kg bw/day considered safe as a food ingredient for pre-school children by EFSA. In the situation where a food supplement might be consumed together with food containing DHC as an ingredient by schoolchildren, the total daily intake at the 97.5th percentile reaches 1.38 mg/kg bw/day when calculated using the most recent NDNS (2008-2011) food consumption data, (March 2013). However, data from the UK NDNS indicate that school children are relatively unlikely to consume non-nutrient supplements such as DHC and so this level of intake is unlikely to occur in reality. Nonetheless, even in this circumstance, the revised total daily intake estimate stays in the same range at 1.38 mg/kg bw/day as that estimated in the original application for pre-schoolers of 1.3 mg/kg bw/day, where the MOS in relation to the NOAEL was considered sufficient by the EFSA Panel (EFSA, 2012).

In consequence, we conclude that such an extension of use of DHC, to include food supplement use, should not raise any safety concerns for the target population.

*as defined by Directive 2002/46/EC (2002) and in Part E of Annex II of Regulation (EC) No 1333/2008; see also **Guidance document describing the food categories in Part E of Annex II to Regulation (EC) No 1333/2008 on Food Additives**, taken from, http://ec.europa.eu/food/food/fAEF/additives/guidance_en.htm

Introduction

In July 2010, Ajinomoto sought approval in Europe under Regulation (EC) No. 258/97 of the European Parliament and of the Council of 27th January 1997 concerning Novel Foods and Novel Food Ingredients, for the use of Dihydrocapsiate (DHC) as a Novel Food Ingredient.

The application was for the approval of DHC in foods that would deliver 3 mg per portion or serving in various food categories, resulting in a mean estimated intake of 12 – 13 mg/day (8.1 mg/day for pre-school children); the 97.5th percentile intakes of adults and the elderly were estimated to be around 34 mg/day (18.5 mg/day for pre-school children). The actual DHC concentration in any food item would therefore depend upon the manufacturer's product specification for single-served products or on typical or recommended portion sizes for products presented in multi-serve packs. These concentration levels would vary from 8 to 2050 mg per kg.

The UK Food Standards Agency acted as the Competent Authority for the initial assessment of DHC as a novel food ingredient. Their Opinion issued on the 25th January 2011 was that,

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

The application and subsequent EU consultation process resulted in the European Commission requesting a scientific opinion from European Food Safety Agency (EFSA) on the safety of synthetic dihydrocapsiate (DHC) as a food ingredient in the context of Regulation (EC) No 258/97, (EFSA, 2012) which stated:

"Considering the proposed uses the estimated mean intake of synthetic DHC was estimated to be around 12 – 13 mg/day (8.1 mg/day for pre-school children); the 97.5th percentile intakes of adults and the elderly were estimated to be around 34 mg/day (18.5 mg/day for pre-school children) based on UK consumption data. Calculations based on body weights resulted in the highest intakes being for pre-school children (mean: 0.6 mg/kg bw/day; 97.5th percentile: 1.3 mg/kg bw/day)."

"Taking account of the estimated intake levels resulting from the uses as proposed by the applicant, the Panel is of the opinion that the margin of safety in relation to the NOAEL of 300 mg/kg bw/day in the 26-week rat toxicity study is sufficient, including the highest estimated intake of 1.3 mg/kg bw/day for preschool children."

"The Panel concludes that the novel food ingredient, DHC, is safe under the proposed uses and use levels."

This opinion together with subsequent consideration resulted in the the following approval:

COMMISSION IMPLEMENTING DECISION of 22 November 2012 authorising the placing on the market of dihydrocapsiate as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (notified under document C(2012) 8391) (2012/726/EU) Official Journal of the European Union L 327/49

The authorised uses for DHC under this decision (as detailed in Annex II) are shown overleaf in Table 1.

Ajinomoto Co., Inc. now wishes to extend its current Novel Foods authorisation for DHC to include its use as a food supplement per Directive 2002/46/EC (2002) and Annex II of Regulation (EC) No 1333/2008 which could be consumed by school children, adolescents, adults and the elderly.

Table 1: Authorised uses of DHC as a food ingredient

Food category	**Maximum use levels**
Cereal bars	9 mg/100 g
Biscuits, cookies and crackers	9 mg/100 g
Rice based snacks	12 mg/100 g
Carbonated drinks, dilutable drinks, fruit juice based drinks	1,5 mg/100 ml
Vegetable drinks	2 mg/100 ml
Coffee based drinks, tea based drinks	1,5 mg/100 ml
Flavoured water — still	1 mg/100 ml
Precooked oatmeal cereal	2,5 mg/100 g
Other cereals	4,5 mg/100 g
Ice cream, dairy desserts	4 mg/100 g
Pudding mixes (ready to eat)	2 mg/100 g
Products based on yoghurt	2 mg/100 g
Chocolate confectionery	7,5 mg/100 g
Hard candy	27 mg/100 g
Sugar-free gum	115 mg/100 g
Whitener/creamer	40 mg/100 g
Sweeteners	200 mg/100 g
Soup (ready to eat)	1,1 mg/100 g
Salad dressing	16 mg/100 g
Vegetable protein	5 mg/100 g
Ready to eat meals Replacement meals	3 mg/meal
Meal replacement drinks	1 mg/100 ml

This submission has been prepared pursuant to the Commission Recommendation (97/618/EC) of 29 July 1997. Under these Guidelines the Applicant considered that DHC should be allocated into Class 1: pure chemicals or simple mixtures from non-GM sources and further classified under sub-class 1.2, the source of the Novel Food has no history of food use in the Community. In line with these recommendations, Sections IV to VIII of the EU recommendations are not applicable to DHC since no GM technology is employed.

Requirements

1.0 Administrative Data

1.1 Name and Address of Applicant/Manufacturer:

The Applicant is AJINOMOTO CO., INC., JAPAN

Wellness Business R&D Planning Department
15-1, Kyobashi 1-choume,
Chuo-ku,
104-8315,
Tokyo, Japan

1.2 Name and Address of Person Responsible for the Dossier:

Mr Takashi Kayahara
AJINOMOTO CO., INC., JAPAN
Wellness Business R&D Planning Department

15-1, Kyobashi1-choume,
Chuo-ku,
104-8315,
Tokyo, Japan

Phone: +81-3-5250-8791
Fax: +81-3-5250-5066
Email: takashi_kayahara@ajinomoto.com
URL: http://www.ajinomoto.com/

1.3 Name and Address of EU Contact for the Dossier Representing AJINOMOTO:

Andrew Cockburn PhD FBS FBTS
UK/EU Registered Toxicologist
Visiting Professor University of Newcastle

Toxico-Logical Consulting Ltd
Gravesend Farm
Albury, Ware
Herts, SG112LW, UK

Phone: +44(0)1279-771-699
Mobile: +44(0)7720-413-169
Fax: +44(0)1279 -771-699
Email: andrew.cockburn@onetel.net

2.0 General Description

2.1 The Product

Ajinomoto Co., Inc is applying to extend its authorisation of synthetic Dihydrocapsiate (DHC) as a novel food ingredient for additional use as a food supplement as defined by Directive 2002/46/EC (2002) and Part E of Annex II of Regulation (EC) No 1333/2008.

DHC was first discovered in a non-pungent chilli pepper, CH-19 Sweet, more than 20 years ago (Yazawa et al., 1989). It is an analogue of capsaicin that does not have the same pungency.

Food supplement levels of DHC of up to 9 mg/day are forseen for consumption by school children, adolescents, adults and the elderly. Pre-school children (infants and young children) have been excluded from this Application in accordance with the above Directive and Part E to Annex II of Regulation (EC) No 1333/2008.

2.2 Current Status of Regulatory Approval

2.2.1 DHC

In the USA, DHC has been determined to be Generally Recognised as Safe (GRAS) through scientific procedures, at both 1 and 3 mg per portion of food based on standard servings[1]. The GRAS Exemption Claims dated April 21st 2008 and December 30th 2009 were reviewed by the Food and Drug Administration (FDA) who provided "no objection" Agency response letters, GRAS Notice No. GRN 000249 and GRAS Notice No. GRN 000312 on March 9, 2009 and June 6, 2010, respectively. The NDI notification dated November 9th 2011 was reviewed by FDA who provided a "no objection" response letter on February 13th, 2012 and filed this as a new dietary ingredient notification report number 739, see Appendix 1. This letter offers "no objection" to dietary supplement use at up to 15mg per day.

GRAS Notice No.GRN 000249:

http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm161407.htm

GRAS Notice No.GRN 000312:

http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm218465.htm

2.2.2 CH-19 Sweet extract (Capsiate Natura™)

Concerning CH-19 Sweet extract that contains approximately 7.5% capsinoids (including approximately 20% DHC in capsinoids)

- In Europe: the Czech Republic officially recorded CH-19 Sweet extract as food supplement (2008)
- In Europe: the French Republic officially recorded CH-19 Sweet extract as foods (including food supplement) (2009)
- In Japan: CH-19 Sweet extract was officially recorded as a food in 2006 and has been on the market as Capsiate Natura™ since then
- In the U.S: FDA provided no objection for notification CH-19 Sweet extract as a New Dietary Ingredient in 2007 and has been on the market since then.

[1] Reference amounts customarily consumed per eating occasion see (21 CFR 101.12)

3.0 Novel Food Categorisation

3.1 Identification of Essential Information Requirements

In 2011, ACNFP (ACNFP Opinion, 2011) concluded that,

"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 according to the scheme in Commission Recommendation 97/618 (EC))."

According to Commission Recommendation 97/618/EC[1], the structured schemes outlined to be followed for the assessment of a Class 1.2 novel food ingredient, are listed below

I. Specification of the novel food

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

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

IV-VIII. Not applicable*

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

XI. Nutritional information on the novel food

XII. Microbiological information on the novel food

XIII. Toxicological information on the novel food

*Since DHC involves no GM technology.

Each structured Decision Tree has been followed sequentially, using the same notation and the resultant questions are responded to point by point under sub-headings for each of the schemes.

However, since this application relates only to an extension of use, and in the absence of any significant new information for Sections I, II, III, XI, XII and XIII, these Sections remain identical to those originally submitted.

In consequence the only newly updated section that has been drafted in support of the extension of Authorisation of DHC as a food supplement is Section IX which considers the potential impact on exposure of the requested Novel Food extension.

[1]Commission Recommendation (97/618/EC) of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment reports under Regulation of (EC) No 258/97 of the European Parliament and of the Council, OJ L253,16.09.

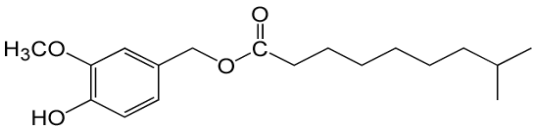
I. Specification of Dihydrocapsiate (DHC)

Based on the Commission Recommendation No 97/618 guidelines, the following questions must be answered to ensure that there is sufficient information on the specification of the novel food:

- *"Is there an appropriate specification (including species, taxon etc. for living organisms) to ensure that the novel food marketed is the same as that evaluated?"*
- *"Is the information representative of the novel food when produced on a commercial scale?"*
- *"Is appropriate analytical information available on potentially toxic inherent constituents, external contaminants and nutrients?"*

These questions have been addressed in Sections I.1 through I.3.

Ajinomoto's product for which novel food ingredient status is sought is subsequently referred to as dihydrocapsiate (DHC). It is a viscous colourless to yellow liquid which is synthesised using high purity (≤ 98% pure) starting materials.

Common or usual name:	DIHYDROCAPSIATE (DHC)
Chemical name :	(4-hydroxy-3-methoxybenzyl) 8-methylnonanoate
Synonym:	Dihydrocapsiate
CAS Number:	205687-03-2
Empirical Formula:	$C_{18}H_{28}O_4$
Structural Formula:	
Molecular Weight :	308.41
Appearance	Viscous, colourless to yellow liquid
Solubility in water	Insoluble in water
Solubility in solvents	Readily soluble in ethanol and hexane

I.1 Is there an appropriate specification (including species, taxon etc. for living organisms) to ensure that the novel food marketed is the same as that evaluated?

The specification for DHC is laid down in Annex 1 of the Commission Implementing Decision of 22nd November 2012 authorising the placing on the market of dihydrocapsiate as a novel food ingredient under Regulation 258/97 of the European parliament and Council, (2012/726/EU). See Table 2 below

Table 2: Specifications of Dihydrocapsiate reproduced from Commission Implementing Decision (EC Commission, 2012)

L 327/50 EN Official Journal of the European Union 27.11.2012

ANNEX I

SPECIFICATIONS OF DIHYDROCAPSIATE

Definition

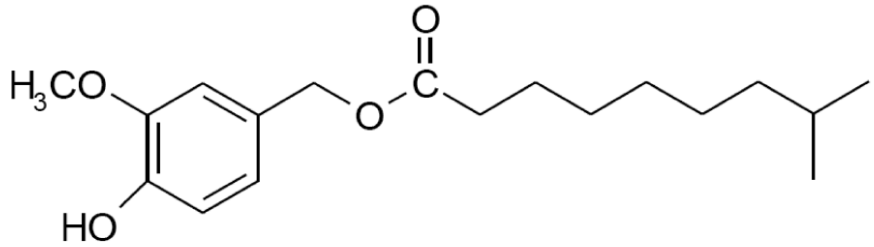
Dihydrocapsiate is synthesised by enzyme-catalysed esterification of vanillyl alcohol and 8-methylnonanoic acid. Following the esterification dihydrocapsiate is extracted with n-hexane.

The enzyme Lipozyme 435 was approved by the Danish Veterinary and Food Administration.

Description: Viscous colourless to yellow liquid

Chemical formula: $C_{18}H_{28}O_4$

Structural formula:



CAS No: 205687-03-2

Physical-chemical properties of dihydrocapsiate

Dihydrocapsiate	more than 94 %
8-Methylnonanoic acid	less than 6 %
Vanillyl acohol	less than 1 %
Synthesis related substances	less than 2 %

I.2 Is the information representative of the novel food when produced on a commercial scale?

EFSA noted, (EFSA Opinion, 2012) that

"The applicant provided compositional data for seven batches (between 10 and 20 kg each lot) of the novel food ingredient produced sequentially on pilot plant scale over a period of 3 months in 2006 (Table 2)."

"The analyses were conducted by two external accredited analytical laboratories which operated either in accordance with Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP), or in compliance with ISO/IEC 17025."

A minimum mass balance of 98.14% was achieved and it was demonstrated that the manufacturing process and final product are highly reproducible, thus the the process is capable of producing material that consistently meets specification, see Table 3 below (reproduced from Table 2, EFSA Opinion, 2012) .

EFSA concluded that, ***''The reaction vessels are made of high grade stainless steel typical of pharmaceutical and food standard manufacturing plants. The scale-up to commercial scale is not considered to impact the quality of the resulting DHC or its ability to comply with the specification of the resulting commercial grade DHC food ingredient."*** **(EFSA Opinion, 2012).*"***

Table 3: Reproduced from EFSA Opinion (2012): Reproducibility of production process

Table 2: Compositional data on seven lots of the novel food ingredient DHC produced at pilot plant scale in the period from June to August 2006

	Lot 060626	Lot 060705	Lot 060712	Lot 060720	Lot 060731	Lot 060807	Lot 060817
Dihydrocapsiate (%)	95.0	95.7	94.2	94.1	93.5	94.0	94.6
Starting materials							
8-Methylnonanoic acid (%)	2.0	2.0	3.3	3.4	5.8	4.3	4.8
Vanillyl alcohol (%)	0.04	0.03	0.03	0.03	< 0.025	< 0.025	< 0.025
Synthesis-related substances (%)	1.10	0.86	0.74	0.69	0.81	1.39	0.75
Vanillyl 6-bromohexanoate (%)	0.07	0.07	n.d.[a]	n.d.	n.d.	0.07	< 0.025
Vanillyl decanoate (%)	0.04	0.04	0.04	0.04	0.04	0.04	0.03
Vanillyl dihydrocapsiate (%)	0.60	0.50	0.48	0.47	0.48	0.73	0.37
Diacyl form (%)	0.14	0.12	0.11	0.09	0.17	0.42	0.24
Others (%)	0.25	0.13	0.11	0.09	0.12	0.13	0.085
Mass balance (% w/w)	98.14	98.59	98.27	98.22	100.11	99.69	100.15
Magnesium (mg/kg)	0.3	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Copper (mg/kg)	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2

[a] not detected

I.3 Is appropriate analytical information available on potentially toxic inherent constituents, external contaminants and nutrients?

It is stated that

"The Panel considers the compositional data provided for the novel food ingredient as sufficient."

(EFSA Opinion, 2012).

II. Effect of the Production Process Applied to the Novel Food Ingredient

Based on the Commission Recommendation No 97/618 guidelines, the following questions must be addressed to ensure sufficient information exists on the production process for the novel food ingredient:

- *"Does the novel food undergo a production process?"*
- *"Is there a history of use of the production process for the food?" If no …*
- *"Does the process result in a significant change in the composition or structure of the NF compared to its traditional counterpart?"*

In the EFSA Opinion, 2012 it is stated that

"*The Panel concludes that the production process is sufficiently described by the applicant and does not raise concerns*."

III. History of the organism used as a source

Based on the Commission Recommendation No 97/618 guidelines, the first question must be addressed to ensure sufficient information pertaining to the history of the original source organism.

- *"Is the novel food obtained from a biological source (i.e., a plant, animal or microorganism)?"*
- *"Has the organism used as the source of the novel food been derived using genetic modification?"*
- *"Is the source organism characterised?"*
- *"Is there information to show that the source organism and/or foods obtained from it are not detrimental to human health?"*

DHC occurs naturally in the human diet as it is present in chilli peppers. It belongs to the chemical family called capsinoids (typically DHC, nordihydrocapsiate and capsiate) which are present in most chilli peppers, which come from the large genus Capsicum.

As the authorised DHC (EC Commission, 2012) which is the subject of this extension request is produced synthetically, EFSA concluded that this Section was

"*Not applicable*"

(EFSA Opinion, 2012).

Sections IV to VIII

Sections VI to VIII of the EU recommendation are not applicable to DHC since no GM technology is involved.

IX Anticipated Intake/Extent of Use of the Novel Food Ingredient and Supplement

Based on the Commission Recommendation No 97/618 guidelines, the following questions must be addressed to ensure sufficient information pertaining to the anticipated intake and extent of use of the novel food:

- *"Is there information on the anticipated uses of the novel food based on its properties?"*
- *"Is there information to show anticipated intakes for groups predicted to be at risk?"*
- *"Will introduction of the novel food be restricted geographically?"*
- *"Will the novel food replace other foods in the diet?"*

These questions have been addressed in Sections IX.1 through IX.5.

IX.1 Authorised Use of DHC as a Novel Food ingredient and proposed extension of use as a Food Supplement

Dihydrocapsiate (DHC) was originally authorised for use in 5 food categories to allow food manufacturers flexibility in product formulation. The categories chosen resulted from discussions between the the Applicant and manufacturers who identified the potential to use DHC in baked goods, beverages, confectionery, cereals and desserts and other miscellaneous foods.

Ajinomoto Co., Inc. produces the food ingredient for use by third party food manufacturers but does not itself manufacture foods containing DHC. As a consequence, the applicant sought approval for the use of DHC that would deliver 3mg per portion or serving.

In this application, Ajinomoto Co., Inc. only wishes to extend the uses currently approved, to the use of DHC as a food supplement* as defined in Directive 2002/46/EC (2002) and Annex II of Regulation (EC) No 1333/2008 at up to 3mg, 3 times a day, ie a total maximum daily intake of 9 mg/individual.

*This category covers pre dosed foodstuffs of which the purpose is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tables, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.

17.1 Food supplements supplied in a solid form including capsules and tablets and similar forms, excluding chewable forms
This category includes supplements in tablet, powder or granule form. It covers inter alia tablets to be dissolved in liquid before consumption (effervescent tablets), pills, pastilles, capsules containing liquids (fish oil supplements) and other forms of powders designed to be taken in measured small unit quantities. It includes chewable tablets.
17.2 Food supplements supplied in a liquid form
This category includes supplements marketed in the form of liquids and to be consumed as liquids, like ampoules of liquids, drop dispensing bottles, and other similar forms of liquids.
17.3 Food supplements supplied in a syrup-type or chewable form
This category includes supplements marketed under the form of syrup or a chewable form (e.g. chewable capsule, jelly-type supplement and other chewable forms, excluding chewable tablets) and intended to be consumed as such.

The use levels that were authorised (EC Commission, 2012) are tabulated below

Table 4: Authorised uses of DHC as a food ingredient (to provide 3 mg per serving)

Food category	**Maximum use levels**
Cereal bars	9 mg/100 g
Biscuits, cookies and crackers	9 mg/100 g
Rice based snacks	12 mg/100 g
Carbonated drinks, dilutable drinks, fruit juice based drinks	1,5 mg/100 ml
Vegetable drinks	2 mg/100 ml
Coffee based drinks, tea based drinks	1,5 mg/100 ml
Flavoured water — still	1 mg/100 ml
Precooked oatmeal cereal	2,5 mg/100 g
Other cereals	4,5 mg/100 g
Ice cream, dairy desserts	4 mg/100 g
Pudding mixes (ready to eat)	2 mg/100 g
Products based on yoghurt	2 mg/100 g
Chocolate confectionery	7,5 mg/100 g
Hard candy	27 mg/100 g
Sugar-free gum	115 mg/100 g
Whitener/creamer	40 mg/100 g
Sweeteners	200 mg/100 g
Soup (ready to eat)	1,1 mg/100 g
Salad dressing	16 mg/100 g
Vegetable protein	5 mg/100 g
Ready to eat meals/Replacement meals	3 mg/meal
Meal replacement drinks	1 mg/100 ml

EFSA, noted in their Opinion (EFSA 2012) that,

"Based on these proposed uses and use levels, the applicant conducted an intake estimation based on individual consumption data collectd by UK NDNS surveys (Office for National Statistics, 2005: UKDA. 1995, 2001). The mean estimated intake of DHC was around 12 -13 mg/day (8.1 mg/day for pre-school children): the 97.5th percentile intakes of adults and the elderly were around 34 mg/day (18.5 mg/day for pre-school children). Calculations based on body weights resulted in the highest intakes being for pre-school children (mean: 0.6 mg/kg bw/day: 97.5th percentile; 1.3 mg/kg bw/day)."

IX. 2 Estimated intakes of DHC as a Food supplement

IX.2.1 Potential DHC intakes based on data in original submission

On the basis of DHC use levels established in the Commission implementing decision (European Commission 2012) and set out in Table 4 of this submission, potential intakes of DHC were modelled for UK consumers in four age groups in a previous ACNFP submission (Table 5). The results were confirmed in the Scientific Opinion from European Food Safety Authority (EFSA) on the safety of synthetic dihydrocapsiate (DHC) as a food ingredient (EFSA, 2012). These estimates represent a conservative scenario because it is assumed that all foods listed in Table 4 would always contain DHC at the maximum stated level.

Table 5: Potential intakes of DHC for UK consumers (1992–2001) from authorised use as a food ingredient, per Ajinomoto (2010) Submission to ACNFP and EFSA Opinion (2012)

Ingredient use	**DHC intake, mg/day**				**DHC intake, mg/kg bw/day**			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children	8.1	13.1	15.7	18.5	0.6	0.9	1.1	1.3
School children	12.8	19.9	23.2	26.2	0.4	0.7	0.8	0.9
Adults	12.3	23.3	29.5	33.8	0.2	0.3	0.4	0.4
Elderly	11.7	23.2	29.2	34.2	0.2	0.3	0.4	0.5

It is proposed to add to the existing authorisation, the use of DHC as a dietary supplement to provide up to 3mg, up to 3 times a day, giving a total maximum daily intake of 9 mg/individual/day. It is considered very unlikely that the supplement would be given on a regular basis to infants and young children and product labels will exclude this use, so potential intakes from this source would be limited to school children, adolescents, adults and the elderly. When expressed on a bodyweight basis, intakes from supplement use only range from 0.04-0.08 mg/kg bw/day at the mean for users of 3mg per day to 0.18-0.52 mg/kg bw/day for users of 9mg per day at the 97.5th percentile (Table 5). Variations within dose groups relate to differences in bodyweight only.

If it is assumed in a 'worst case' scenario, that an individual would choose to take the maximum amount of the proposed supplement (9mg) in addition to intake from the use of DHC as a food ingredient as described in Table 5, then the maximum total exposure can be estimated from the original food consumption estimates and bodyweight data (Table 6).

Table 6: Potential intakes of DHC (mg/kg bw/day) resulting from daily supplement consumption giving 3, 6 or 9 mg DHC per day by all consumers (1992-2001).

Supplement use:	**3 mg/day**				**6 mg/day**				**9 mg/day**			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	0.08	0.15	0.16	0.17	0.17	0.30	0.33	0.35	0.25	0.45	0.49	0.52
Adults	0.04	0.05	0.06	0.06	0.08	0.11	0.11	0.12	0.12	0.16	0.17	0.18
Elderly	0.05	0.06	0.07	0.07	0.09	0.12	0.13	0.14	0.14	0.18	0.20	0.21

Table 7: Maximum total potential intakes of DHC for UK consumers (1992–2001) from use as a food ingredient plus maximum use as a food supplement (9mg).

Ingredient use	DHC intake, mg/day				DHC intake, mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children*	8.1	13.1	15.7	18.5	0.6	0.9	1.1	1.3
School children	21.8	28.9	32.2	35.2	0.65	1.15	1.29	1.42
Adults	21.3	32.3	38.5	42.8	0.32	0.46	0.57	0.58
Elderly	20.7	32.2	38.2	43.2	0.34	0.48	0.60	0.71

* No supplement use in pre-school children

In this scenario, intakes at the 97.5th percentile could reach 1.42 mg/kg bw/day but for this to occur in reality it would be necessary for schoolchildren to consume foods containing DHC at the maximum levels reported in Table 5 and in addition for them to consume daily, three, 3 mg supplements of DHC.

However, the UK food consumption data used to prove intake estimates in Tables 5 and 6 date from surveys undertaken between 1992 and 2001 (Gregory et al, 1995, Finch 1998, Gregory, 2000 and Henderson et al, 2002). Since that time the UK Department of Health has introduced a rolling programme of annual Nation Diet and Nutrition Surveys that cover all age groups. The most recent set of results cover three years between 2008 and 2011 and are available to download (National Centre for Social Research, accessed February 2014). The latest NDNS surveys now include data on food supplement consumption and so can be used to model potential intakes by actual supplement users in addition to potential intakes from food ingredient use of DHC.

IX2.2 Potential DHC intakes based on 2008 – 2011 UK food consumption data

It is expected that the normal consumer would typically eat several portions of one type of food containing DHC to obtain their daily intake of the food ingredient. However, there could be exceptional circumstances in which a consumer consumed more than one type of product containing DHC. Furthermore, although DHC products would be targeted at adults, there could be circumstances in which children might consume the foods if they are available for household use. Since children have higher food consumption than adults on a bodyweight basis, their intake of DHC could be correspondingly higher.

Because it is not yet known which of the potential food categories will be selected by food manufacturers to present DHC to the market, a hypothetical worst-case scenario has again been adopted which assumes that all of the potential food applications contain sufficient DHC to provide 3 mg DHC from an average serving of food, as set out in Table 4. In reality it is unlikely that the market would support such a diverse range of food applications and so the resulting estimates of intake will necessarily over-estimate true potential exposures.

The proposed additional use of DHC as a dietary supplement to provide up to 3mg, up to 3 times a day, giving a total maximum daily intake of 9 mg/individual/day can be added to total intake from food ingredient use as was done for the older data (see Table 5 and 6) to provide a revised and updated 'worst case' scenario. Alternatively the database can be applied in such a way that only those individuals who reported consumption of dietary supplements during the food consumption surveys are assumed to be potential consumers of DHC supplements.

To estimate DHC intakes it is assumed that all foods in the UK NDNS database that fall into the categories proposed for DHC addition would contain a sufficient concentration of DHC to deliver 3mg from an average portion of the food as defined in Table 4. Each individual's intake of DHC is then calculated for each occasion that he or she consumes any of the foods (by multiplying the DHC concentration by the quantity of food consumed) and the total amount is then divided by the number of days in the survey and the individual's reported bodyweight. Intake estimates are subdivided by age group to provide data for pre-school children (1-4 yrs), schoolchildren (5-10 yrs), adolescents (11-17 yrs), adults (18 – 64 yrs) and the elderly (65+ yrs).

Intakes from supplement use only are calculated by assigning a supplement level (3, 6, or 9mg) to each individual and then dividing this amount by his or her individual bodyweight. This can be done either for all individuals (apart from small children) or for only those who reported food supplement use. To calculate total intakes from food ingredient use and supplements, a daily amount (3, 6, or 9mg) is added to each

individual's average daily intake from food ingredient use, either for all individuals (apart from infants and young children) or for only those who reported food supplement use.

IX.2.2.1 Intakes from food ingredient use

Potential intakes of DHC for UK consumers from authorised use as a food ingredient based on 2008-2011 NDNS data, range from 0.13 mg/kg/day at the mean for elderly consumers up to 1.09 mg//kg bw/day at the 97.5th percentile for pre-school children (Table 8). Potential intakes from food ingredient use appear to have fallen by up to one third in some cases between the periods of the earlier NDNS surveys and the most recent data. The decline appears to affect adults more, and schoolchildren the least. This could be a reflection of changing eating habits amongst the adult population relating to either less frequent consumption of certain foods or to smaller portions when consumed.

Table 8: Potential intakes of DHC for UK consumers (2008-2011) from authorised use as a food ingredient.

Ingredient use	**mg/day**				**mg/kg bw/day**			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children	7	12	15	16	0.48	0.83	0.99	1.09
Schoolchildren	9	16	18	19	0.39	0.66	0.78	0.90
Adolescents	12	19	23	27	0.22	0.40	0.47	0.54
Adults	10	20	24	28	0.14	0.27	0.33	0.38
65+	10	18	23	26	0.13	0.25	0.32	0.36

IX.2.2.2 Intakes from food supplement use

If intakes of DHC from possible supplement use are considered separately, and it is assumed that the entire population (with the exception of pre-school children) will be supplement users, then all individuals would have a daily intake of 3, 6 or 9 mg. The only other source of variation in this scenario would arise from differences in bodyweight (Table 9).

Table 9: Potential intakes of DHC resulting from daily supplement consumption giving 3, 6 or 9 mg DHC per day for all consumers (2008-2011).

Supplement use:	**3 mg/day**				**6 mg/day**				**9 mg/day**			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	0.13	0.17	0.18	0.19	0.25	0.33	0.36	0.39	0.38	0.50	0.54	0.58
Adolescents	0.06	0.08	0.09	0.10	0.12	0.16	0.18	0.20	0.17	0.25	0.28	0.31
Adults	0.04	0.05	0.06	0.06	0.08	0.11	0.11	0.12	0.12	0.16	0.17	0.18
65+	0.04	0.05	0.06	0.06	0.08	0.11	0.11	0.12	0.12	0.16	0.17	0.18

(mg/kg bw/day)

However, not all individuals will be users of food supplements and the 2008-11 NDNS survey is able to provide an indication of the proportion of the survey population who reported supplement use (Table 10). Individuals reporting some supplement use, including vitamins and minerals, during the period of the survey ranged from 8% in adolescents to 38% in the elderly. In the UK NDNS database 'non-nutrient' and 'other' food supplements include products such as kelp tablets, soya protein, royal jelly and rosehip extract. Less than 1% of school or pre-school children were reported to consume non-nutrient food supplements. This confirms the expectation that DHC as a non-nutrient supplement would not be regularly consumed as a food supplement by infants and young children, and product labels will exclude this use. Potential intakes for all

supplement users are provided in Table 11. Intakes for this group are very similar to the intake for the entire population suggesting that they have representative bodyweights. However they represent a much smaller number of consumers.

Table 10: Proportion of individuals in UK NDNS survey 2008-2011 who reported consumption of any food supplement.

Age group	Subjects in survey	All supplements	%	Non - nutrient and other supplements	%
Pre-school children	261	32	12%	2	<1%
Schoolchildren	514	93	18%	2	<1%
Adolescents	644	54	8%	4	<1%
Adults	1179	279	24%	105	9%
65+	282	108	38%	58	21%
All	2880	566	20%	171	6%

Table 11: Intakes of DHC resulting from daily supplement consumption giving 3, 6 or 9 mg DHC per day only by consumers of food supplements (2008-2011)

Supplement use:	**3 mg/day**				**6 mg/day**				**9 mg/day**			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	0.13	0.17	0.18	0.19	0.26	0.34	0.35	0.38	0.39	0.51	0.53	0.58
Adolescents	0.06	0.09	0.11	0.11	0.13	0.19	0.21	0.22	0.19	0.28	0.32	0.33
Adults	0.04	0.05	0.06	0.06	0.08	0.11	0.12	0.12	0.13	0.16	0.17	0.18
65+	0.04	0.05	0.06	0.06	0.08	0.11	0.11	0.12	0.12	0.16	0.17	0.18

(mg/kg bw/day)

IX.2.2.3 Total intakes from food ingredient and supplement use

Total intakes from use of DHC as a food ingredient and as a food supplement can be calculated for the entire population or assuming DHC supplement use by food supplement users only. Adding food supplement use at 3, 6 or 9 mg per day to intake from food ingredient uses for all consumers (excluding pre-school children) provides a range of potential intakes ranging from 0.13 mg/kg bw/day on average for the elderly resulting from food ingredient use only, up to 1.38 mg/kg bw at the 97.5th percentile for schoolchildren taking daily supplements containing 9 mg in addition to intakes from food ingredient use (Table 12).

This assessment represents an extreme worst case scenario based on 2008-2011 NDNS data because school children are unlikely to consume non-nutritional and other supplements (see Table 10) and in order to achieve this level of intake it would be necessary for their diet to be comprised only of foods containing DHC at maximum levels for all categories for which it is approved and for them to take a supplement of 9mg every day.

Table 12: Maximum potential total* intakes of DHC resulting from food ingredient use and daily supplement consumption giving 3, 6 or 9 mg DHC per day by all consumers (2008-2011)

Food ingredient use only,

no supplement

	mg/day				mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children*	7	12	15	16	0.48	0.83	0.99	1.09
Schoolchildren	9	16	18	19	0.39	0.66	0.78	0.90
Adolescents	12	19	23	27	0.22	0.40	0.47	0.54
Adults	10	20	24	28	0.14	0.27	0.33	0.38
65+	10	18	23	26	0.13	0.25	0.32	0.36

Food ingredient plus 3 mg/day supplement

	mg/day				mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children	-	-	-	-	-	-	-	-
Schoolchildren	12	19	21	22	0.51	0.81	0.93	1.07
Adolescents	15	22	26	30	0.28	0.46	0.54	0.62
Adults	13	23	27	31	0.18	0.32	0.38	0.42
65+	13	21	26	29	0.17	0.29	0.36	0.41

Food ingredient plus 6 mg/day supplement

	mg/day				mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children	-	-	-	-	-	-	-	-
Schoolchildren	15	22	24	25	0.64	0.96	1.07	1.22
Adolescents	18	25	29	33	0.34	0.54	0.62	0.72
Adults	16	26	30	34	0.22	0.36	0.42	0.47
65+	16	24	29	32	0.21	0.34	0.41	0.46

Food ingredient plus 9 mg/day supplement

	mg/day				mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Pre-school children	-	-	-	-	-	-	-	-
Schoolchildren	18	25	27	28	0.76	1.10	1.24	1.38
Adolescents	21	28	32	36	0.40	0.62	0.69	0.81
Adults	19	29	33	37	0.26	0.40	0.47	0.52
65+	19	27	32	35	0.25	0.38	0.47	0.52

** Estimates of total intake are not necessarily the sum of intakes of food ingredient intakes and food supplement intakes because the 95th percentile consumer from each food source will be differnet and different again to the 95th percentile consumer from both sources combined.*

A more realistic, yet still conservative, intake scenario can be based on information from the NDNS dietary surveys about consumers who report food supplement consumption. In this case intake of DHC from

supplement use is added only to those consumers who reported consumption of food supplements during the survey. Adding food supplement use at 3, 6 or 9 mg per day to intake from food ingredient uses for supplement users only provides a range of potential intakes ranging from 0.13 mg/kg bw/day on average for the elderly up to 1.08 mg/kg bw at the 97.5th percentile for schoolchildren (Table 13). Population intake estiamtes are lower in this scenario because the proportion of the population who take food supplements is taken into account.

Table 13: Potential total* intakes of DHC based on approved food ingredient use levels for the entire population plus supplementation at 3, 6 or 9 mg/day for users of food supplements only

Food ingredient us only, no supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	9	16	18	19	0.39	0.66	0.78	0.90
Adolescents	12	19	23	27	0.22	0.40	0.47	0.54
Adults	10	20	24	28	0.14	0.27	0.33	0.38
65+	10	18	23	26	0.13	0.25	0.32	0.36

Food ingredient plus 3 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	10	17	19	20	0.41	0.71	0.79	0.93
Adolescents	12	20	23	27	0.23	0.41	0.48	0.56
Adults	11	21	25	29	0.15	0.29	0.35	0.40
65+	11	19	24	28	0.14	0.27	0.35	0.40

Food ingredient plus 6 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	10	17	19	22	0.43	0.73	0.85	0.97
Adolescents	12	20	24	27	0.23	0.42	0.49	0.57
Adults	12	22	26	30	0.16	0.31	0.37	0.42
65+	12	21	26	29	0.16	0.29	0.37	0.41

Food ingredient plus 9 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	11	18	20	24	0.45	0.80	0.92	1.08
Adolescents	12	21	26	29	0.24	0.42	0.52	0.61
Adults	12	24	28	31	0.16	0.33	0.39	0.44
65+	3	23	28	32	0.18	0.32	0.41	0.46

** Estimates of total intake are not necessarily the sum of intakes of food ingredient intakes and food supplement intakes because the 95th percentile consumer from each food source.*

In the final assessment, users of food supplements have been considered as a separate sub-group. Intakes at the 97.5th percentile for consumers of 9 mg DHC supplement daily remain below 1.3 mg/kg bw /day for all age groups (Table 14). Some differences are apparent between the intakes for the sub-group of supplements users (Table 13) and the total population (Table 11) which relate to intakes from food ingredient use and variataions in bodyweight, but they are probably not significant.

Table 14: Intakes of total* intake DHC (mg/kg bw/day) resulting from food ingredient use and daily supplement consumption giving 3, 6 or 9 mg DHC per day only by consumers of non-nutrient supplements

Food ingredient use only, no supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	9	16	18	20	0.38	0.61	0.75	0.86
Adolescents	12	20	20	24	0.26	0.47	0.53	0.62
Adults	11	20	24	30	0.16	0.29	0.35	0.40
65+	10	20	23	30	0.14	0.26	0.33	0.37

Food ingredient plus 3 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	12	19	21	23	0.50	0.77	0.90	0.99
Adolescents	15	23	23	27	0.32	0.55	0.63	0.70
Adults	14	23	27	33	0.20	0.33	0.39	0.44
65+	13	23	26	33	0.18	0.32	0.38	0.42

Food ingredient plus 6 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	15	22	24	26	0.61	0.92	1.05	1.13
Adolescents	18	26	26	30	0.38	0.63	0.72	0.79
Adults	17	26	30	36	0.24	0.38	0.44	0.50
65+	16	26	29	36	0.22	0.38	0.42	0.48

Food ingredient plus 9 mg/day supplement

	mg/day				mg/kg bw/day			
Age band	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Schoolchildren	17	25	27	29	0.73	1.09	1.21	1.28
Adolescents	21	29	29	33	0.44	0.71	0.83	0.88
Adults	20	29	33	39	0.28	0.43	0.47	0.55
65+	19	29	32	39	0.26	0.43	0.46	0.53

* Estimates of total intake are not necessarily the sum of intakes of food ingredient intakes and food supplement intakes because the 95th percentile consumer from each food source.

IX.3 Is there information to show anticipated intakes for groups predicted to be at risk?

Since no single intake for existing or proposed uses of DHC will exceed more than 3mg, and maximum potential intake from all sources is unlikely to exceed 1.38 mg/kg bw/day, we do not believe that any population groups will be at risk. Notwithstanding, the product is not intended (and will be off-label) for pre-school infants and young children and NDNS survey data indicate further that the consumption of supplements by school children is very uncommon.

IX.4 Will introduction of the novel food br restricted geographically?

Approval is sought for the novel food ingredient to be available in foodstuffs throughout Europe. There are no proposed geographical restrictions.

IX.5 Will the novel food replace other foods in the diet?

It is not considered that it will replace other foods.

IX.6 Food Product Labelling Information

An appropriate and clear designation (name) representing dihydrocapsiate (DHC) or formulated products containing DHC shall be displayed on the labelling of the product as such, or in the list of ingredients of foodstuffs containing it.

To comply with the definition of a food supplement as defined by Directive 2002/46/EC (2002) and in Part E of Annex II of Regulation (EC) No 1333/2008, labelling will exclude food supplements for infants and young children.

IX.7 Conclusion on anticipated Dihydrocapsiate Intakes

Intakes of DHC from its authorised use as a food ingredient have been re-calculated using more recent UK survey data. This has resulted in a small decrease in the intake of DHC from this source and the highest level has fallen from 1.3 mg/kg bw/day for pre-schoolchildren at the 97.5th percentile based on data from 1992-2001 to 1.1 mg/kg bw/day for the same age group in 2008-11.

Adding a dietary supplement to provide up to 3mg, up to 3 times a day, giving a total maximum daily intake of 9 mg/individual/day, to the potential intake from food ingredient use gives a highest maximum total intake of 1.42 mg/kg bw/day at the 97.5th percentile based on 1998 schoolchildren's data or 1.38 mg/kg bw/day for schoolchildren based on 2008-11 food consumption data. However, data from the UK NDNS indicate that schoolchildren are unlikely to consume non-nutrient food supplements and so this level of intake is unlikely to occur in reality.

XI Nutritional Information

Based on the Commission Recommendation No 97/618 guidelines, the following questions must be answered in the affirmative to ensure sufficient nutritional information pertaining to the nutritional information of the novel food:

- *"Is there information to show that the novel food is nutritionally equivalent to existing foods that it might replace in the diet?"*

This question has been addressed in Section XI.1.

XI.1 Nutritional Equivalence to Existing Foods

EFSA, concluded in their Opinion (EFSA 2012) that,

"DHC manufactured by Ajinomoto is identical to the dihydrocapsiate found as a component of the capsinoids contained in Capsicums. The Panel considers that both synthetically produced DHC and DHC naturally occurring in the diet do not have a nutritionally relevant role in the human diet, and that the consumption of the novel food ingredient is not nutritionally disadvantageous."

XII. Microbiological Information

Based on the Commission Recommendation No 97/618 guidelines, the following question must be addressed to ensure sufficient microbiological information on the novel food:

- *"Is the presence of any microorganisms or their metabolites due to the novelty of the product/process?"*

This question is briefly addressed below and has been covered earlier in Section I.3.5 of this application.

XII.1 Microbiological Information (see Section I.3.5)

EFSA, concluded in their Opinion (EFSA 2012) that,

"The data provided do not raise concerns with regards to a microbial risk."

XIII. Toxicological and Human Safety Information

Based on the Commission Recommendation No 97/618 guidelines, the following questions must be addressed to ensure sufficient information pertaining to the toxicology of the novel food ingredient:

- *"Is there a traditional counterpart to the novel food that can be used as a baseline to facilitate the toxicological assessment?"*
- *"is there information from a range of toxicological studies appropriate to the novel food to show that the novel food is safe under anticipated conditions of preparation and use?"*
- *"is there information which suggests that the novel food might pose an allergenic risk to humans?"*

These questions have been addressed in Sections XIII.1 to XIII.3, respectively.

XIII.1 Is there a traditional counterpart?

There is no free, stand-alone traditional counterpart to synthetic dihydrocapsiate (DHC). However, small amounts of natural DHC, which is chemically identical to synthetic DHC, have been consumed over many centuries from Capsicums due to their content of capsinoids which are made up of DHC, together with capsiate and nordihydrocapsiate.

XIII.2 Toxicological and Human Health Assessment of DHC

EFSA, concluded in their Opinion (EFSA 2012) that regarding the animal toxicology,

"The applicant has provided a range of toxicological studies with DHC. The Panel concludes that it has no safety concerns regarding genotoxicity. Studies on developmental toxicity in rats and rabbits using commercial grade DHC did not show adverse effects on pregnant animals or on foetal growth and development. The no-observed adverse effect level (NOAEL) of three subchronic oral toxicity studies in rats was consistently at 300 mg DHC/kg bw/day."

and regarding the human studies…

"*The Panel is of the opinion that the human studies are of little relevance for the safety assessment since they were of short duration, the administered doses were low, and the number of safety endpoints studied was limited."*

XIII.3 Potential Allergenicity Concerns for Humans

EFSA, concluded in their Opinion (EFSA 2012) that

"Although no studies on allergenicity were provided by the applicant, the Panel considers that it is unlikely that the novel ingredient poses an allergenic risk."

XIII.4 Safety Assessment

These questions were addressed and discussed in the original dossiers and the most recent opinions of ACNFP and EFSA concluded as follows.

XIII.4.1 Determination of the no-observed-adverse-effect–level (NOAEL)

ACNFP Opinion (2011)

"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."

EFSA Opinion (2012)

"The no-observed adverse effect level (NOAEL) of three subchronic oral toxicity studies in rats was consistently at 300 mg DHC/kg bw/day."

XIII 4.2 Determination of the safety factor and safe level of intake

ACNFP Opinion (2011)

"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."

EFSA Opinion (2012)

"The Panel is of the opinion that the margin of safety (MOS) in relation to the NOAEL of 300 mg/kg bw/day is sufficient, including the highest estimated intake of 1.3 mg/kg bw/day for pre-school children."

XIII 4.3 Margin of Safety for consumers from food ingredient and/or food supplement use

a) Food ingredient use - as authorised (EC Commission, 2012)

EFSA Opinion (2012)

"Taking account of the estimated intake levels resulting from the uses as proposed by the applicant, the Panel is of the opinion that the margin of safety in relation to the NOAEL of 300 mg/kg bw/day in the 26-week rat toxicity study is sufficient, including the highest estimated intake of 1.3 mg/kg bw/day for pre-school children."

Table 15: Showing Estimated intakes* based on use levels providing 3 mg of DHC in an average portion for adults (reproduced from EFSA Opinion, (2012), page 12)

	DHC intake, mg/day				DHC intake, mg/kg bw/day			
Age group	Mean	P90	P95	P97.5	Mean	P90	P95	P97.5
Adults	12.3	23.3	29.5	33.8	0.2	0.3	0.4	0.4
Pre-school children	8.1	13.1	15.7	18.5	0.6	0.9	1.1	1.3
School children	12.8	19.9	23.2	26.2	0.4	0.7	0.8	0.9
Elderly	11.7	23.2	29.2	34.2	0.2	0.3	0.4	0.5

*For consumers only

b) <u>Food supplement use – requested as an extension to the above existing authorisation.</u>

On the basis that each individual consumes supplement(s) containing up to 9 mg on a daily basis, their absolute intake will be 9 mg/day. When modelled, it was found that consumption of the food supplement alone by schoolchildren, who have the highest bodyweight related intake, gave a 97.5th percentile intake estimate of only 0.58 mg/kg bw/day which is well below the 1.3mg/kg bw/day considered safe as a food ingredient for pre-school children by EFSA. In the situation where a food supplement might be consumed together with food containing DHC as an ingredient by schoolchildren, the total daily intake at the 97.5th percentile reaches 1.38 mg/kg bw/day when calculated using the most recent NDNS (2008-2011) food consumption data, (March 2013). However, data from the UK NDNS indicate that school children are unlikely to consume non-nutrient supplements such as DHC and so this level of intake is unlikely to occur in reality. Nonetheless, even in this circumstance, the revised total daily intake estimate stays in the same range at 1.38 mg/kg bw/day as that estimated in the original application for pre-schoolers of 1.3 mg/kg bw/day, where the MOS in relation to the NOAEL was considered sufficient by the EFSA Panel (EFSA, 2012).

CONCLUSION

Taking the conclusions of ACNFP and EFSA into account from their assessment of DHC as a novel food ingredient together with new exposure modelling to examine the impact of the proposed extension of use to a food supplement, it can be seen that:-

1. The exposure estimates would typically be approximately 50% lower for exclusive food supplement use than those associated the use of DHC as a novel food ingredient.

2 In an extreme worse case scenario where it is assumed that all individuals who consumed foods containing DHC as an ingredient also consumed a supplement of up to 9mg/day, the highest intake at the 97.5th percentile based on most recent data is for school children who would be estimated to consume 1.38 mg/k bw/day. This figure is comparable to the exposure value of 1.3 mg/kg bw/day for pre-school children consuming DHC as a food ingredient that the EFSA Panel considered to be sufficient (EFSA, 2012).

3 The specific risk management and labelling provisions laid down by the Commission Directive 2002/46 on food supplements (European Parliament and the Council of the European Union, 2002) together with Part E of Annex II to Regulation (EC) No 1333/2008 will manage the levels proposed in food supplements.

4. Both food and food supplement uses combined, as an extreme worst case scenario, for the potentially highest intake group due to body weight, namely schoolchildren who would be estimated to consume 1.38 mg/kg bw/day, continue to result in a wide margin of safety (MOS) of >200 fold in relation to the to the NOAEL of 300mg/kg bw/day.

Based on the exposure assessment resulting from anticipated use of DHC as a food supplement, and taking into account the existing safety data, it is concluded that DHC food supplement use does not represent a significant risk for human health at the estimated intake levels which are either lower or if combined with food ingredient use comparable to, those which already do not raise safey concerns for EFSA, (EFSA, 2012).

GLOSSARY

Capsinoids – a family of related substances principally including dihydrocapsiate, nordihydrocapsiate and capsiate, qv E-capsiate

CAS – Chemical Abstracts Service No.

CFSAN – Centre for Food and Drug Safety and Applied Nutrition

CH-19 SWEET EXTRACT – An oily extract from the Sweet Pepper CH-19 containing dihydrocapsiate, nordihydrocapsiate and capsiate

DHC – Dihydrocapsiate

EFSA – European Food Standard Authority (Europe)

FDA – Food and Drug Administration (USA)

FSA – Food Standards Agency (UK)

GRAS – Generally Recognised As Safe (USFDA status term for foods having a demonstrated history of safe use)

JP – Japanese Pharmacopoeia

JSFA – Japan's Specifications and Standards for Food Additives

MNA – 8-Methyl Nonanoic Acid

MOE – Margin Of Exposure

MOS – Margin Of Safety

MSDS – Material Safety Data Sheet

NDNS – National Diet and Nutritional Survey (UK)

NOAEL – No-observed-adverse-effect-level

V- OH – Vanillyl Alcohol

REFERENCES

ACNFP Opinion, (2011) Advisory Committee on Novel Foods and Processes - Draft opinion on an application under the novel foods regulation for synthetic dihydrocapsiate for 10 day public consultation, 25th January, 2011

Ajinomoto (2010) Application for the Approval of Dihydrocapsiate (DHC) for use as a novel food ingredient. Submitted to ACNFP in July 2010 pp1-93

Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards the use of certain food additives in food supplements for infants and young children

Guidance document describing the food categories in Part E of Annex II to Regulation (EC) No 1333/2008 on Food Additives, 18th December 2013.

Accessed 30th April 2014 at http://ec.europa.eu/food/food/fAEF/additives/docs/guidance_1333-2008_descriptors_annex2_20131218_en.pdf and taken from...

http://ec.europa.eu/food/food/fAEF/additives/guidance_en.htm, accessed 30th April 2014

Commission recommendation (97/618/EC) of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the preparation of initial assessment report under Regulation of (EC) No 258/97 of the European Parliament and of the Council.

Directive 2002/46/EC (2002) Of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, Official Journal of the European Communities L 183/51

EC Commission, (2012) Commission of the European Communities, Commission Decision of 22 November 2012 authorising the placing on the market of dihydrocapsiate as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (notified under document C(2012) 8391) (2012/726/EU). *Official Journal of the European Union 27.11.2012, L 327/49*

EFSA. (2008) European Food Safety Authority. Guidance Document for the use of the Concise European Food Consumption Database in Exposure Assessment. EFSA/DATEX/2008/01. Parma, 17 March 2008.

EFSA Opinion, (2012) Scientific opinion from European Food Safety Agency (EFSA) on the safety of synthetic dihydrocapsiate (DHC) as a food ingredient in the context of Regulation (EC) No 258/97, EFSA Journal 2012;10(7):2812

Gregory, J. R., Collins, D.L., Davies, P.S.W., Hughes, J.M. and Clarke, P.C. (1995). National Diet and Nutrition Survey; Children aged 1½ to 4½ years. HMSO, London.

Gregory J. (2000) National Diet and Nutrition Survey: young people aged 4 to 18 years. Findings: Volume 1. London: The Stationery Office.

Finch, S. (1998). National diet and nutrition survey people aged 65 years and over. The Stationery Office. ISBN: 0112430198.

Henderson, L., Gregory, J. and Swan, G. (2002). The National Diet and Nutrition Survey: adults aged 19 to 64 years. Types and quantities of foods consumed. Her Majesty's Stationery Office (HMSO). ISBN 0 11 621566 6.

National Centre for Social Research, Medical Research Council. Resource Centre for Human Nutrition Research and University College London. Medical School, National Diet and Nutrition Survey, 2008-2011 [computer file]. 5th Edition. Colchester, Essex: UK Data Archive [distributor], March 2013. SN: 6533 , http://dx.doi.org/10.5255/UKDA-SN-6533-4

NDI (Pre-Market Notification for New Dietary Ingredient) (2007) CH-19 Sweet Extract (Containing Capsinoids in the Extracted Oil of Sweet chilli Pepper) 21st February 2007, Ajinomoto, USA Inc.

Regulation (EC) No 258/97 of the European Parliament and of the Council of 27th January 1997 concerning novel foods and novel food ingredients OJ L43,14.02.1997

USFDA Agency Response 'No Objection' Letter GRAS Notice No. GRN 000249, CFSAN/Office of Food Additive Safety, March 9, 2009

http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/ucm161407.htm

USFDA Agency Response 'No Objection' Letter GRAS Notice No.GRN 000312, CFSAN/Office of Food Additive Safety, June 6th, 2010

http://www.fda.gov/Food/IngredientsPackagingLabeling/GRAS/NoticeInventory/ucm218465.htm

Yazawa,S.,Suetome, N., Okamoto, K., and Namiki T (1989) Content of Capsaicinoids and Capsaicinoid-like substances in fruit of pepper(capskum annuum L.) hybrids made with 'CH-19 Sweet' as a parent. J. Japan. SOC. Hod. Sci. 58:601-607

Appendix 1

Synthetic DHC 'no objection' letter in response to NDI notification of DHC at up to 15 mg a day

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

FEB 1 3 2012

Ashish Talati
Amin Talati, LLC
225 North Michigan Avenue, Suite 700
Chicago, Illinois 60137

Dear Mr. Talati:

This is to inform you that the notification, dated November 9, 2011, which you submitted on behalf of Ajinomoto North America, Inc, pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was received and filed by the Food and Drug Administration (FDA) on November 14, 2011. Additional information was filed on January 25, 2012. The information received on January 25, 2012 was a substantive amendment and you received a letter, dated January 27, 2012 which reset the filing date to January 25, 2012. Your notification concerns synthetic "dihydrocapsiate" which you identify as a new dietary ingredient and intend to market as a dietary ingredient.

Your notification provides the following conditions of use: "will be marketed as dietary ingredient with a maximum daily intake of 15 mg."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Under 21 CFR 190.6(5)(d) if the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient, provides additional information in support of the new dietary ingredient notification, the agency will review all submissions pertaining to that notification, including responses made to inquiries from the

continued overleaf

agency, to determine whether they are substantive and whether they require that the 75-day period be reset. If the agency determines that the new submission is a substantive amendment, In accordance with 21 CFR 190.6 (c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains the new dietary ingredient that is the subject of this notification.

Please note that acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredients or supplement that contains the new dietary ingredients are safe or are not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredients if they are found to be unsafe, adulterated or misbranded.

Your notification will be kept confidential for 90 days after the filing date of January 25, 2012. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number FDA-1995-S-0039 (formerly docket number 95S-036) as a new dietary ingredient notification report number 739. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter please contact Dr. Fred Hines, Consumer Safety Officer for the New Dietary Ingredient Review Team, at (240) 402-1756.

Sincerely yours,

Ramadevi Gudi

Ramadevi Gudi, Ph.D.
Acting New Dietary Ingredient Review Team Leader
Division of Dietary Supplement Programs
Office of Nutrition, Labeling and Dietary Supplements
Center for Food Safety and Applied Nutrition