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CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 7a **CX/FA 16/48/15**

February 2016

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD ADDITIVES

Forty-eighth Session

Xi'an, China, 14-18 March 2016

PROPOSALS FOR ADDITIONS AND CHANGES TO THE PRIORITY LIST OF SUBSTANCES PROPOSED FOR EVALUATION BY JECFA

Comments (replies to CL 2015/11-FA) of European Union, Japan, Sudan, Switzerland, United States of America, CEFIC, ETA, IACM, and ISDI

EUROPEAN UNION

The European Union and its Member States are proposing to add the following substances to the priority list of substances proposed for evaluation by JECFA:

i **INS 1203 Polyvinyl alcohol** – request for amendment of the JECFA monograph as regards solubility in ethanol

ii **Alpha-amylase from Bacillus licheniformis expressing a modified alpha-amylase gene from Geobacillus stearothermophilus** – request for safety assessment and establishment of specifications

iii **Prolyl endopeptidase from Aspergillus niger expressing a gene from Aspergillus niger** – request for safety assessment and establishment of specifications

iv **Phosphatidyl inositol-specific phospholipase C from a genetically modified strain of Pseudomonas fluorescens** – request for safety assessment and establishment of specifications

v **Transglucosidase/alpha-glucosidase from Trichoderma reesei expressing an Alpha-glucosidase Gene from Aspergillus niger** – request for safety assessment and establishment of specifications

vi **Amyloglucosidase from Talaromyces emersonii expressed in Aspergillus niger** – request for safety assessment and establishment of specifications

vii **Beta-amylase from Bacillus flexus expressed in Bacillus licheniformis** – request for safety assessment and establishment of specifications

viii **Lactase from Bifidobacterium bifidum expressed in Bacillus licheniformis** – request for safety assessment and establishment of specifications

ix **Lipase from Aspergillus oryzae expressing a modified gene from Thermomyces lanuginosus** – request for safety assessment and establishment of specifications

x **INS 1205, Basic Methacrylate Copolymer** – Safety evaluation and establishment of specification when used as glazing / coating agent.

xi **INS 1206, Neutral Methacrylate Copolymer** – Safety evaluation and establishment of specification when used as glazing / coating agent.

xii **INS 1207, Anionic Methacrylate Copolymer** – Safety evaluation and establishment of specification when used as glazing / coating agent.

Enclosures:

The forms containing information on the substances mentioned above.

PROPOSAL I - INS 1203 Polyvinyl alcohol

Name of Substance(s):	**POLIVINYL ALCOHOL (PVOH) - CAS 9002-89-5**
Question(s) to be answered by JECFA (Kindly provide a brief justification of the request in case of re-evaluations)	**Request to change the JECFA monograph: solubility of PVOH in ethanol from "sparingly soluble in ethanol" to "practically insoluble or insoluble in ethanol (≥ 99,8 %)"**

1. Proposal for inclusion submitted by: JONES DAY, Rue de Régence 4, 1000 Brussels

2. Name of substance; trade name(s); chemical name(s): Polyvinyl alcohol

3. Names and addresses of basic producers: Nippon Synthetic Chemical Industry

4. Has the manufacturer made a commitment to provide data? Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person): Ales Bartl, email: abartl@jonesday.com, Tel: 0032 2 645 1452

6. Justification for use: Existing food additive (INS 1203) used as a glazing agent or thickener

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s): 13.6 Food supplements, 45000 mg/kg

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies)): Approved for use in the EU in food supplements supplied in a solid form permitted at 18000 mg/kg only in capsule and tablet form

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

(iii) Epidemiological and /or clinical studies and special considerations

(iv) Other data

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

The Institute for Health and Consumer Protection (IHCP) of the European Commission's Joint Research Centre carried out solubility studies of polyvinyl alcohol to update the solubility data of the existing Union specifications vis-à-vis its solubility in ethanol.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Other information (as necessary/identified)

10. Date on which data could be submitted to JECFA: Immediately

Data supporting the request:
- two copies of solubility tests

- copy of Regulation (EU) 2015/463 of 19 March 2015 amending Annex to Regulation (EU) No 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council as regards specifications for polyvinyl alcohol (E 1203)

PROPOSAL II - Alpha-amylase from *Bacillus licheniformis* expressing a modified alpha-amylase gene from *Geobacillus stearothermophilus*

Name of Substance(s):	**Alpha-amylase from *Bacillus licheniformis* expressing a modified alpha-amylase gene from *Geobacillus stearothermophilus***
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid.

1. Proposal for inclusion submitted by:

The Danish Veterinary and Food Administration
Head Office
Att: Jytte Kjaergaard
Stationsparken 31-33
DK 2600 Glostrup
Tel. +45 72 27 69 00

2. Name of substance; trade name(s); chemical name(s):

Name of substance: Alpha-amylase from *Bacillus licheniformis* expressing a modified Alpha-amylase Gene from *Geobacillus stearothermophilus*

Trade names: SPEZYME ALPHA, SPEZYME CASSAVA (main commercial names)

Chemical names: IUBMB 3.2.1.1 and CAS number 9000-90-2

3. Names and addresses of basic producers:

Danisco US Inc. (operating as DuPont Industrial Biosciences)
925 Page Mill Road
Palo Alto, CA 94304
UNITED STATES
Tel.: +1 650 846 7500

4. Has the manufacturer made a commitment to provide data?

DuPont Industrial Biosciences (Danisco US Inc.) commits to provide data to support the proposal for inclusion of the alpha-amylase in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Danisco US Inc. (operating as DuPont Industrial Biosciences)
925 Page Mill Road
Palo Alto, CA 94304
UNITED STATES
Tel.: +1 650 846 7500
Attn.: Lisa Jensen, Regulatory Affairs Consultant
lisa.jensen@dupont.com +45 89435564; Alternative/Copy: mirjam.rademaker@dupont.com

6. Justification for use:

The food enzyme catalyses the endohydrolysis of (16 7500pha-D-glucosidic linkages in polysaccharides containing three or more (1500-alpha-linked D-glucose units with the main reaction products being maltodextrins, maltooligosacharides and glucose.

GC 358 (used as the general code for this enzyme product) contains a thermostable starch hydrolyzing alpha-amylase. It quickly reduces the viscosity of gelatinized starch, producing soluble dextrins and oligosaccharides under a variety of process conditions.

For grain processors, it offers the following benefits:

- Quick viscosity reduction allowing for higher solids
- Liquefaction pH's as low as 5.2
- Process flexibility
- Improved performance at low slurry temperatures

Industry specific benefits:

For starch processors: GC 358 rapidly lowers viscosity of gelatinized starch and allows therefore processing at high solid levels. This offers significant energy savings in the concentration of the final products by evaporation.

For ethanol producers: GC 358 reduces the viscosity of grain mashes rapidly and allows processing of high mash solids.

For brewing operators: GC 358 reduces the viscosity of the unmalted cereals rapidly allowing for high mash solids.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

GC 358 is intended for carbohydrate processing for the manufacture of HFCS (High Fructose Corn Syrups), cassava starch processing, wheat starch processing, cane sugar processing, and brewing and potable alcohol manufacture.

To obtain the desired effects of this enzyme, the recommended dose is 0.2 - 0.6 kg enzyme preparation/MT starch in accordance with current Good Manufacturing Practices (cGMPs).

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

The enzyme preparation containing Alpha-amylase produced with this production organism is approved in the following countries:

France: The enzyme has been approved for its safety in France. It has passed already the European TRIS procedure, as can be seen here http://ec.europa.eu/growth/tools databases/tris/en/search/?trisaction=search.detail&year=2015&num=308

(End of Standstill: 17/09/2015). (See attachment)

The publication in the French Official Journal is expected on short run.

9. List of data available (please check, if available)

The production organism is from a safe strain as described in the decision tree in Pariza and Johnson, 2001[1]. However, to accommodate various registration requirements in different countries world-wide, a full toxicity program for food enzymes has been performed according to the SCF guidelines for the evaluation of food enzymes[2].

Toxicological data

(i) Metabolic and pharmacokinetic studies - Not applicable.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

The following studies have been conducted in accordance with internationally accepted guidelines (OECD/EU/FDA) and do not give any concerns:

- Acute oral toxicity in rats – Fixed dose procedure
- Sub-chronic 13 week toxicity in the rat
- Bacterial reverse mutation assay (Ames assay)
- In vitro mammalian cell gene mutation test(L5178/TK+/- Mouse Lymphoma Assay)
- In vitro mammalian cell micronucleus assay in human peripheral blood lymphocytes

The conclusion of the safety studies can be summarized as follows:

The safety of GC 358 is assessed in a battery of toxicology studies investigating its acute oral, genotoxic and systemic toxicity potential. GC 358 is not acutely toxic by ingestion. Daily administration of GC 358 by gavage for 90 continuous days did not result in overt signs of systemic toxicity. A battery of genotoxicity assays was conducted and under the conditions of these assays GC 358 is not a mutagen or a clastogen.

(iii) Epidemiological and/or clinical studies and special considerations - Not applicable.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

The product conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing as prepared by the Joint FAO/WHO Expert Committee on Food Additives at its sixty-seventh meeting for publication in FAO JECFA Monographs 3 (2006) and to the acceptance criteria, impurity limits, other test and other requirements for enzyme preparations listed in the Food Chemicals Codex, 9th edition.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

The alpha-amylase enzyme preparation from *Bacillus licheniformis* GC 358 will be used as a processing aid in starch processing and in the manufacture of beer and potable alcohol. It quickly reduces the viscosity of gelatinized starch, producing soluble dextrins and oligosaccharides under a variety of process conditions. The action of the enzyme takes place at the beginning of the process to hydrolyse the starch for further processing. This step is followed by several steps of liquefaction and saccharification. The boiling process will inactivate the enzyme. No enzyme will be present in the end product due to distillation in the case of potable alcohol product.

Alpha-amylase is a protein and any residual amounts remaining in food consumed would have the same nutritional value accordingly. However, the use levels of Alpha-amylase are very low. As with other enzymes that are currently approved and used as processing aids, use of this product would have an insignificant impact on the nutritional value of the food.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

GC 358 is intended for carbohydrate processing for the manufacture of HFCS, cassava starch processing, wheat starch processing, cane sugar processing, and brewing and potable alcohol manufacture.

The proposed application rates of GC 358 are:

Cassava starch processing = 0.2 to 0.3 kg enzyme preparation/MT starch

[1] Pariza MW, Johnson EA; Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century; Regul Toxicol Pharmacol 2001 Apr;33 (2):173-86.
[2] Opinion expressed by the Scientific Committee for Food on 11 April 1991, http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_27.pdf

Wheat starch processing = 0.4 to 0.6 kg enzyme preparation/MT starch

Brewing and alcohol processing = 0.2 to 0.45 kg enzyme preparation/MT starch

Carbohydrate processing = 0.2 to 0.45 kg enzyme preparation/MT starch

Cane sugar processing = 5 ppm active enzyme/MT starch

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Based on the conservative calculation by means of the Budget method, based on an application of GC 358 containing 9.35% TOS at the maximum rate of 0.6 kg GC 358/MT starch, the maximum human daily intake of TOS from processed liquid foods (non-milk) and solid foods containing GC 358 is 0.315 mg TOS/kg bw/day.

Other information (as necessary/identified) - None

10. Date on which data could be submitted to JECFA - As soon as necessary.

Attachment: *"Attachment_Application GC 358 JECFA_Avis de l'Anses_25FEB15"*

OPINION of the French Agency for Food, Environmental and Occupational Health & Safety on the application for authorisation to use an alpha-amylase derived from a strain of genetically modified *Bacillus licheniformis* carrying the alpha-amylase coding gene of *Geobacillus stearothermophilus* for brewing, starch manufacturing, glucose syrup production and the potable alcohol industry

ANSES implements independent and pluralistic scientific expert appraisals.

ANSES's principle mission is to ensure environmental, occupational and food health and safety, and to assess the potential health risks in these areas.

It also contributes to the protection of the health and welfare of animals, and the protection of plant health, as well as to the evaluation of the nutritional properties of food.

It provides the relevant authorities with the necessary information concerning these risks as well as the required expertise and scientific support for developing laws and regulations and implementing risk management strategies (Article L.1313-1 of the French Public Health Code).

Its opinions are made public.

On June 3, 2014, ANSES received a request from the Directorate General for Competition, Consumption and Repression of Fraud (DGCCRF) to carry out the following expert appraisal: Request for opinion on the application for authorisation to use an alpha-amylase derived from a strain of genetically modified *Bacillus licheniformis* carrying the alpha-amylase coding gene of *Geobacillus stearothermophilus* for brewing, starch manufacturing, glucose syrup production and the potable alcohol industry.

Further to the expert appraisal of the dossier on an opinion request regarding the application for authorisation to use an alpha-amylase derived from a strain of genetically modified *Bacillus licheniformis* carrying the alpha-amylase coding gene of *Geobacillus stearothermophilus* for brewing, starch manufacturing, glucose syrup production and the potable alcohol industry, ANSES delivered a negative decision on April 18, 2012, due to uncertainties regarding the genotoxicity of the food enzyme and a need to further support the safety margin calculation.

On June 3, 2014, additional information provided by the petitioner was delivered to ANSES by the DGCCRF, leading to the reconsideration of this request.

The expert appraisal was carried out in accordance with French standard NF X 50-110 « Quality in Expertise – General Requirements of Competence for Expert Appraisals (May 2003) »

Further to the « Biotechnology » Working Group meeting on July 17 and October 28, 2014, ANSES presented two requests to the DGCCRFfor additional information on July 23 and November 3, 2014. These were addressed on October 14 and January 13, 2015, respectively, allowing to continue with the expert appraisal.

The collective expert appraisal was conducted based on the five appraisal reports by the « Biotechnology » Working Group which met on July 17, 2014, October 28, 2014 and February 18, 2015.

This dossier falls within the framework of the decree of May 10, 2011[3] setting out the conditions for authorisation and use of the processing aids which can be utilised in the production of foodstuffs intended for human consumption.

According to Article 1 of the March 7, 2011[4] statement, the dossier should be prepared following the EFSA guidance[5] for the dossier submission on food enzymes.

ANSES analyses interests declared by experts before they are appointed and throughout their assignment in order to prevent risks of conflicts of interest in relation to the points addressed in expert appraisals. The experts' declarations of

[3]Decree No 2011-529 of May 10th 2011, setting out the conditions for authorisation and use of processing aids employed in the manufacturing of foodstuffs intended for human consumption.
[4]Statement of March 7th 2011, regarding the guidelines for the compilation of application dossiers for the authorisation of use of processing aids for human food.
[5]Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids on the Submission of a Dossier on Food Enzymes. *The EFSA Journal*(2009), 1305:1-26.

interests are made public on ANSES's website (www.anses.fr).

3.1 Genotoxicity data

The genotoxicity tests presented during the first application [reverse mutation test on five strains of histidine-dependent *Salmonellatyphimurium* (Ames test) and chromosomal aberration test on cultured human peripheral lymphocytes] implemented lower food enzyme doses than doses traditionally recommended by the OECD. The mutagenic and clastogenic effects observed in these two tests were small but statistically significant. The unusual cytotoxicity and the genotoxicity test anomalies observed at the relatively low levels of enzyme doses tested therefore did not enable to reach a decision on the safety of this food enzyme (opinion of April 18, 2012, request 2011-SA-0240).

In this new dossier, three new studies were carried out: one reverse mutation test on four strains of histidine-dependent *Salmonellatyphimurium* and one mutant strain of *Escherichia coli* (Ames test), one *in vitro* gene mutation test on mouse thymic lymphoma cells, and one *in vitro* micronucleus test on human peripheral lymphocytes. These studies were conducted in accordance with the international guidelines of the OECD[6] and in compliance with Good Laboratory Practice.

The petitioner indicated having conducted these three new studies using the same batch of food enzymes as the first two studies presented in the initial request (request 2011-SA-0240). The three studies were carried out at different doses of the experimental product (food enzyme), with and without the S9-based metabolic activation system and using the appropriate positive and negative controls.

The new bacteria reverse mutation study (Ames test on four strains of histidine-dependent *Salmonellatyphimurium* and one tryptophan-dependent strain of *Escherichia coli*) is carried out at enzyme concentrations up to 5000 цд/ЬоТ1е(maximum recommended dose as per the OECD guidelines) with the S9-based metabolic activation system and of 500 цд/Ьойе without the S9-based metabolic activation system. No increase in number of revertant colonies is observed in the presence of the food enzyme and therefore the study does not show any mutagenic effect.

Irrespective of the enzyme dose applied (up to 250 pg/ml without and up to 5000 pm/ml with the S9-based system), the *in vitro* gene mutation study on L5178Y/TK$^{+/"}$ mouse thymic lymphoma cells does not show an increase in mutation frequency greater than 90 mutants per million cells, which is a positivity criteria for this test. The food enzyme does not show a mutagenic effect in this study.

The *in vitro* micronucleus test on human peripheral lymphocytes does not show a significant difference in percentage of binucleated cells with micronucleus between treated cells and controls, irrespective of the dose and condition tested (up to 500 pg/ml without and up to 5000 pm/ml with the S9-based system). The food enzyme therefore does not exhibit any clastogenic effects in the conditions tested.

The results of these three studies indicate that the food enzyme does not have genotoxic potential.

A difference in cytotoxicity is observed for the same batch of enzyme used, between the studies for the initial dossier and the three new studies presented. The comparison between the full analysis report of the enzyme tested in the initial dossier and the one carried out in 2014 shows the high stability of this batch of enzyme. The differences in experimental conditions used for the Ames test and the implementation of the two individual *in vitro* tests of the initial dossier can explain the cytotoxicity differences observed between the studies of the initial dossier and the three new ones.

3.2 Dietary exposure

Estimation of the maximum consumption level of the enzyme is calculated using the Budget method by taking into account the consumption level of foodstuffs excluding beverages (except for milk) at 50 g/kg body weight/day and a proportion of 25% of such foodstuffs consumed daily by the general population treated by the enzyme at the maximum recommended dose with a completely preserved enzyme activity. The consumption level of beverages (except for milk) is estimated at 100 ml/kg body weight/day. In this case, as the enzyme is designed only for use in distilled alcoholic beverages, a proportion of 10% of the daily consumption of foodstuffs is retained, taking into consideration that these are treated by the enzyme at the maximum recommended dose with a completely preserved enzyme activity.

The no observed effect level, established in the toxicity study at 90 days in rats (66.81 mg TOS/kg body weight/day) divided by the maximum consumption level of the enzyme via solid and liquid foodstuffs allows to calculate a safety margin of 109.

3.3 Conclusion of the Working Group

In view of the results provided and the terms and conditions presented by the petitioner, the « Biotechnology » Working Group has not identified any health risk factors for the consumer with regards to the use of this alpha-amylase derived from a genetically modified strain of *Bacillus licheniformis* carrying the alpha-amylase coding gene of *Geobacillus stearothermophilus* (strain H03305bQ) for brewing, starch manufacturing, glucose syrup production and the potable alcohol industry.

3.4 Agency conclusion and recommendations

In view of the results provided and the terms and conditions presented by the petitioner, the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) has not identified a health risk for the consumer with regards to the use of this alpha-amylase derived from a genetically modified strain of *Bacillus licheniformis* carrying the alpha-amylase coding gene of *Geobacillus stearothermophilus* (strain H03305bQ) for brewing, starch manufacturing, glucose syrup production and the potable alcohol industry. ANSES therefore provides a favourable opinion for this request.

[6]Organisation for Economic Cooperation and Development.

PROPOSAL III - Prolyl endopeptidase from Aspergillus niger expressing a gene from Aspergillus niger

Name of Compound(s):	**Acid prolyl endopeptidase from a genetically modified strain of *Aspergillus niger***
Question(s) to be answered by JECFA *(kindly provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid.

1. Proposal for inclusion submitted by:

Ministry of Health, Welfare and Sport
Nutrition, Health Protection and Prevention Department
Parnassusplein 5
2511 VX, The Hague
P.O. box 20350
2500 EJ The Hague
The Netherlands
Tel: +31 703407132

2. Name of compound; trade name(s); chemical name(s):

Name of compound: Acid prolyl endopeptidase from a genetically modified strain of *Aspergillus niger*

Trade names: BREWERS CLAREX®, MAXIPRO PSP

Chemical name: Acid prolyl endopeptidase (EC 3.4.21.xx[7])

3. Names and addresses of basic producers:

DSM Food Specialties
5 Rue des Comtesses
PO Box 239
59472 Seclin Cédex
France.
Tel: 33 320964545
Fax: 33 320964500

4. Has the manufacturer made a commitment to provide data? - Yes.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Dr Jack Reuvers
Regulatory Affairs
DSM Food Specialties
PO Box 1
2600 MA Delft
The Netherlands
Tel: +31 15279
Fax: +31 152793614
E-mail: Jack.reuvers@dsm.com

6. Justification for use:

The enzyme preparation is used in beer brewing, potable alcohol production, protein processing and starch processing to catalyze the cleavage of peptide bonds in proteins and peptides, mainly at the carboxylic site of proline residues. The technological need of the enzymatic conversion of proteins and peptides with the help of acid prolyl endopeptidase in these applications can be described as:

- Brewing: degradation of the substrate (proteins and peptides) which otherwise may cause haze in the final product, and to reduce the amount of gluten (gliadins);
- Potable alcohol production: creation of reaction products (smaller peptides) for optimal development of the fermentation;
- Protein processing: degradation of the substrate (proteins and peptides) to obtain a protein hydrolysate without bitter taste;
- Starch processing: degradation of the substrate (proteins and peptides) which would have otherwise a negative influence on the production process, and to reduce the amount of gluten (gliadins) which otherwise might end up in the processed starch product.

[7] The name proline endopeptidase is also a synonym of prolyl oligopeptidase, EC (IUBMB) number 3.4.21.26. However, in contrast to oligopeptidases, the enzyme also acts on proteins (Edens *et al.,* 2005; Kubota *et al.*, 2005; Takahashi, 2013).

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):

The enzyme preparation is used as processing aid in beer brewing, potable alcohol production, protein processing and starch processing in accordance with current Good Manufacturing Practice (cGMP). The dosage of the enzyme varies depending on the specific application:

- Brewing: between 0.7 and 2.1 mg Total Organic Solids (TOS)/kg wort
- Potable alcohol production: between 70 and 704 mg Total Organic Solids (TOS)/kg cereals (dry matter)
- Starch processing: between 0.21 and 3.5 mg Total Organic Solids (TOS)/kg liquefied starch
- Protein processing: between 10000 and 15000 Total Organic Solids (TOS)/kg protein (dry matter)

8. Is the compound currently used in food that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in food in one or more country? (please identify the country(ies))

The enzyme preparation containing acid prolyl endopeptidase derived from a genetically modified strain of *Aspergillus niger* is authorized in the following countries:

Australia/New Zealand: Food Standard 1.3.3 on Processing Aids

Brazil: Diário Oficial da União 2009

China: Food Safety National Standards for the Usage of Food Additives, GB 2760-2011

France: Afssa – Saisine n° 2005-SA-0002

Denmark: Certificate number 2005-20-5406-00080/IM

Mexico: Diario Oficial 2012 (Anexo VI)

Russia: Certificate number RU.77.99.26.009.E.005410.03.11

9. List of data available (please check, if available)

The production organism is from a safe strain as described in the decision tree in Pariza and Johnson, 2001[8]. However, to accommodate various registration requirements in different countries world-wide, a full toxicity program for food enzymes has been performed according to the OECD guidelines/EFSA guidelines for the evaluation of food enzymes[9].

Toxicological data

(i) Metabolic and pharmacokinetic studies - Not applicable.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

The following studies have been conducted in accordance with internationally accepted guidelines (OECD/EU):

- Test for mutagenic activity (Ames test)
- Chromosomal aberration test (*in vitro*)
- 90-days oral toxicity study in rats

The conclusion of the safety studies can be summarized as follows:

The enzyme from a genetically modified *Aspergillus niger* shows no mutagenic and clastogenic activity.

90-days oral administration of the enzyme to rats did not cause in dose related findings. Therefore, the highest dose administered, 5040 mg TOS/kg body weight/day, is considered as the NOAEL.

(iii) Epidemiological and/or clinical studies and special considerations - Not applicable.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

The product conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing as prepared by the Joint FAO/WHO Expert Committee on Food Additives at its sixty-seventh meeting for publication in

[8] Pariza MW, Johnson EA; Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century; Regul Toxicol Pharmacol 2001 Apr; 33(2):173-86.

[9] Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal, 1305, 1-26.
http://www.efsa.europa.eu/en/efsajournal/doc/1305.pdf

FAO JECFA Monographs 3 (2006) and to the acceptance criteria, impurity limits, other test and other requirements for enzyme preparations listed in the Food Chemicals Codex, 9th edition.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The enzyme preparation from genetically modified *Aspergillus niger* will be used as processing aid in beer brewing, potable alcohol production, protein processing and starch processing. The action of the enzyme present in the preparation takes place in a particular process step depending on the application.

In brewing, the food enzyme is typically added to the cooled wort at the beginning of the fermentation step. During pasteurization, acid prolyl endopeptidase will be party denatured. Due to depletion of the substrate, the remaining non-denatured enzyme molecules will not exert a technological function in the final brewing product, just like other enzymes that are produced by the brewers yeast and able to partly survive the pasteurization step.

In potable alcohol production, the food enzyme is added during the pre-saccharification and fermentation steps. During the distillation process, the enzyme proteins are completely removed. Consequently, no acid prolyl endopeptidase activity will be present in the final potable alcohol.

In protein processing, the food enzyme is typically added at the very beginning of the hydrolysis process. During the sterilization step, the enzyme protein is denatured.

In starch processing, the food enzyme is typically added during the saccharification step. During the heating steps, the enzyme protein is denatured.

Taken together, no residual enzyme activity remains in the final product of all applications. The use of the enzyme preparation as processing aid has no influence on the nutritional properties of the final product.

Intake assessment data

(i) Levels of the listed compound used in food or expected to be used in food based on technological function and the range of foods in which they are used.

- Brewing: based on the dose of 0.7- 2.1 mg TOS/kg wort and the fact that 1 L wort results in 1 L, the amount of TOS in the final product will be 0.7- 2.1 mg TOS/ L beer.
- Potable alcohol production: based on the fact that during the distillation process all the TOS will be eliminated, it is assumed that nothing of the TOS will end up in the final product
- Starch processing for beverages: based on the dose of 0.21-3.5 mg TOS/kg liquefied starch and assuming that the ratio from starch hydrolysate to glucose syrup is 0.93 and the ratio from glucose syrup to soft drinks is 0.2, the total ratio will be 0.93x0.2=0.186 and therefore the amount of TOS in the final product will be 0.04-0.65 mg TOS/L soft drink
- Starch processing for solid foods: based on the dose of 0.21-3.5 mg TOS/kg liquefied starch and assuming that the ratio from starch hydrolysate to glucose syrup is 0.93 and the ratio from glucose syrup to confectionery (including candies) is 0.7, the total ratio will be 0.93x0.7=0.65 and therefore the amount of TOS in the final product will be 0.14-2.28 mg TOS/kg jams, biscuits, confectionery, ice cream, etc.
- Protein processing: based on the dose of 10000-15000 TOS/kg protein (dry matter) and assuming that the maximal dose of protein hydrolysates in food is 8.5%, the amount of TOS in the final product will be 850-1275 mg TOS/kg soups, protein shakes, dressings, etc.

(ii) Estimation of dietary intakes based on food consumption data for foods in which the compound may be used.

Based on the conservative calculation by means of the Budget method, assuming that the daily intake of processed foods is 50% of the total solid food intake, i.e. 0.0125 kg/kg bw/day and that the daily intake of soft drinks (assuming that beer is consumed in the same amount as soft drinks) is 25% of the total beverages intake, i.e. 0.025 l/ kg bw/day, and calculating on basis of the **maximal** values found in food and beverage (in the above cases beer and foods containing protein hydrolysates), the total daily intake will be 10.64– 16.0 mg TOS/kg bw/day.

Other information as necessary - None.

10. Date on which data could be submitted to JECFA: As soon as necessary.

PROPOSAL IV - Phosphatidyl inositol-specific phospholipase C from a genetically modified strain of Pseudomonas fluorescens

Name of Compound(s):	**Phosphatidyl inositol-specific phospholipase C from a genetically modified strain of *Pseudomonas fluorescens***
Question(s) to be answered by JECFA *(kindly provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid.

1. Proposal for inclusion submitted by:

Ministry of Health, Welfare and Sport
Nutrition, Health Protection and Prevention Department
Parnassusplein 5
2511 VX, The Hague
P.O. box 20350
2500 EJ The Hague
The Netherlands
Tel: +31 703407132

2. Name of compound; trade name(s); chemical name(s):

Name of compound: Phosphatidyl inositol-specific phospholipase C from a genetically modified strain of *Pseudomonas fluorescens*

Trade names: Purifine SB4, Purifine SB5, Purifine 3G

Chemical names: Phosphatidyl inositol-specific phospholipase C (EC 3.1.4.11)

3. Names and addresses of basic producers:

DSM Food Specialties
15 Rue des Comtesses
PO Box 239
59472 Seclin Cédex
France
Tel: 33 320964545
Fax: 33 320964500

4. Has the manufacturer made a commitment to provide data? - Yes.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Dr Mariella Kuilman
Regulatory Affairs Manager
DSM Food Specialties
PO Box 1
2600 MA Delft, The Netherlands
Tel: +31 (0) 15 2793592
Fax: +31 (0) 15 2793614
E-mail: Mariella.kuilman@dsm.com

6. Justification for use:

The enzyme Phosphatidyl inositol-specific phospholipase C hydrolyzes phosphatidylinositol present in vegetable oil resulting in the formation of diacylglycerol and phophorylinositol. Phosphatidylinositol can negatively impact taste, color and stability of the vegetable oil while diacylglycerol and phosphorylinositol do not have that effect. The removal of phosphatidylinositol with the help of this enzyme preparation may be of benefit in oil refining to give a higher oil yield at lower cost and a lower environmental impact compared to conventional refining methods.

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):

The enzyme preparation is used as processing aid in oil degumming in accordance with current Good Manufacturing Practice (cGMP). The dosage of the enzyme varies between 30 to 300 grams of enzyme preparation per metric ton of oil depending on the specific application.

8. Is the compound currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the compound been approved for use in food in one or more country? (Please identify the country(ies))

The enzyme preparation containing phosphatidyl inositol-specific phospholipase C from a genetically modified strain of *Pseudomonas fluorescens* is authorized/allowed in the following countries:

- USA : GRN 574
- Argentina
- Canada
- EU (except Denmark, France and Spain)

Besides, the enzyme preparation containing phosphatidyl inositol-specific phospholipase C from a genetically modified strain of *Pseudomonas fluorescens* is under evaluation in the following countries:

- Brazil
- Mexico

9. List of data available (please check, if available)

The production organism is from a safe strain as described in the decision tree in Pariza and Johnson, 2001[10]. However, to accommodate various registration requirements in different countries world-wide, a full toxicity program for food enzymes has been performed according to the OECD guidelines and EFSA guidelines for the evaluation of food enzymes[11].

Toxicological data

(i) Metabolic and pharmacokinetic studies - Not applicable.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

The following studies have been conducted in accordance with internationally accepted guidelines (OECD/EU):

- Test for mutagenic activity (Ames Test)
- Chromosomal aberration test, *in vivo*
- 13 weeks oral toxicity in rats

The conclusion of the safety studies can be summarized as follows:

The enzyme from genetically modified *Pseudomonas fluorescens* shows no mutagenic and clastogenic activity.

13 weeks oral administration of the enzyme to rats did not cause any dose related findings. Therefore, the highest dose administered, 2000 mg test substance/kg body weight/day which is 1838 mg TOS/kg body weight/day is considered as the NOAEL.

(iii) Epidemiological and/or clinical studies and special considerations - Not applicable.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

The product conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing as prepared by the Joint FAO/WHO Expert Committee on Food Additives at its sixty-seventh meeting for publication in FAO JECFA Monographs 3 (2006) and to the acceptance criteria, impurity limits, other test and other requirements for enzyme preparations listed in the Food Chemicals Codex, 9th edition.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The enzyme preparation from genetically modified *Pseudomonas fluorescens* will be used as processing aid in oil degumming. In degumming of vegetable oils, the enzyme will end up in water phase whereas the oil is the product phase that will end up in final food applications. Hence, no enzyme activity remains in the final food. The use of the enzyme preparation as processing aid has no influence on the nutritional properties of the final product.

Intake assessment data

(i) Levels of the listed compound used in food or expected to be used in food based on technological function and the range of foods in which they are used

The dosage of the enzyme varies between 30 to 300 grams of enzyme preparation per metric ton of oil depending on the specific application.

(ii) Estimation of dietary intakes based on food consumption data for foods in which the compound may be used.

In the case of oil degumming, the TOS will not end up in the final product since the enzyme TOS will end up completely in the water phase whereas the oil phase is the product of interest.

Other information as necessary - None

10 Date on which data could be submitted to JECFA - As soon as necessary.

[10] Pariza MW, Johnson EA; Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century; Regul Toxicol Pharmacol 2001 Apr;33(2):173-86.

[11] Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal, 1305, 1-26.
http://www.efsa.europa.eu/en/efsajournal/doc/1305.pdf

PROPOSAL (V) - Transglucosidase/alpha-glucosidase from Trichoderma reesei expressing an Alpha-glucosidase Gene from Aspergillus niger

Name of Substance(s):	**Transglucosidase/alpha-glucosidase from *Trichoderma reesei* expressing an Alpha-glucosidase Gene from *Aspergillus niger***
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid.

1. Proposal for inclusion submitted by:

The Danish Veterinary and Food Administration
Head Office
Att: Jytte Kjaergaard
Stationsparken 31-33
DK 2600 Glostrup
Tel. +45 72 27 69 00

2. Name of substance; trade name(s); chemical name(s):

Name of the Substance	**classification 1**	**classification 2**
	Transglucosidase	**Alpha-glucosidase**
Enzyme name	1,4-alpha-glucan 6-alpha- glucosyltransferase	Alpha glucosidase
Other name	Oligoglucan-branching glucosyltransferse	Acid maltase, glucoinvertase, etc
Systematic name	(1 → 4)-alpha-D-Glucan:(1 → 4)-alpha-D-glucan (D-glucose) 6-alpha-D-glucosyltransferase	Alpha-D-Glucoside glucohydrolase
IUBMB No	2.4.1.24	3.2.1.20
CAS No	9030-12-0	9001-42-7
Reaction	Hydrolysis and transfer an alpha-D-glucosyl units of oligosaccharides and convert 1,g glucosidic linkage to 1,6 glucosidic linkages	Hydrolysis of terminal, non-reducing (1->4)-linked alpha-D-glucose residues with release of alpha-D-glucose
Trade Names	TRANSGLUCOSIDASE L-2000, FERMENZYME TL (main commercial names)	

3. Names and addresses of basic producers:

Danisco US Inc. (operating as DuPont Industrial Biosciences)
925 Page Mill Road
Palo Alto, CA 94304
UNITED STATES
Tel.: +1 650 846 7500

4. Has the manufacturer made a commitment to provide data?

Danisco US Inc. (operating as DuPont Industrial Biosciences) commits to provide data to support the proposal for inclusion of transglucosidase and α-glucosidase in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Danisco US Inc. (operating as DuPont Industrial Biosciences)
925 Page Mill Road
Palo Alto, CA 94304
UNITED STATES
Tel.: +1 650 846 7500
Attn.:Vincent J. Sewalt, PhD, Senior Director, Product Stewardship & Regulatory vincent.sewalt@dupont.com
+1 650 846 5861

6. Justification for use:

The food enzyme catalyzes both hydrolytic and transfer reactions on incubation with α-D-gluco-oligosaccharides.

Transfer occurs most frequently to HO-6, producing isomaltose from D-glucose, and panose from maltose. The transfer can also occur to the HO-2 or HO-3 of D-glucose to form kojibiose or nigerose, or back to HO-4 to form maltose. The action on maltose produces equimolar concentration of panose and glucose.

As the result of α-glucosidase-transglucosidase reactions, the malto-oligosaccharides are converted to isomalto-oligosaccharides containing high proportions of glucosyl residues linked by an α-D-1,6 linkage from the non-reducing end.

In addition, the enzyme also hydrolyzes the terminal, non-reducing (1,4)-linked alpha-D-glucose residues with release of alpha-D-glucose.

In molasses, non-fermentable sugars including raffinose and stachyose are converted to sucrose, galactose, glucose and fructose, which can then be fermented into alcohol.

Industrial specific benefit:

For Isomalto-oligosaccharides (IMO) syrup production

- Convert the malto-oligosaccharides in starch to isomalto-oligosaccharides
- The only method to produce IMOs from starch to general knowledge

For potable alcohol, lysine, lactic acid and monosodium glutamate (MSG) processing:

- Convert the malto-oligosaccharides in starch from grains to isomalto-oligosaccharides
- Convert non-fermentable sugars including raffinose and stachyose into sucrose, galactose, glucose and fructose to be fermented
- Increase productivity
- Potential for higher alcohol yield
- Potential for use of less raw material

The effect of the enzymatic conversion is not noticeable in the final food.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Transglucosidase/α-glucosidase enzyme preparation is intended for use in the production of isomalto-oligosaccharides and in the manufacture of potable alcohol, lysine, lactic acid and MSG.

To obtain the desired effects of this enzyme, the recommended dose is as follows in accordance with current Good Manufacturing Practices (cGMPs):

- IMO production: 0.5-1.5 kg enzyme preparation/MT Dry Starch
- Potable alcohol process: 6-20 g enzyme preparation/MT Dry starch
- Lysine, lactic acid and MSG: 4 kg enzyme preparation/MT Dry starch

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

The enzyme preparation containing transglucosidase/α-glucosidase produced with this production organism is legally traded in the following countries:

- USA: GRAS Notice GRN 315

http://www.accessdata.fda.gov/scripts/fdcc/?set=GRASNotices&id=315&sort=GRN_No&order=DESC&startrow=1&type=basic&search=315

- EU (except France, Denmark) based on due diligence and status as processing aid.
- South Korea (based on formal approval)

9. List of data available (please check, if available)

The production organism is from a safe strain as described in the decision tree in Pariza and Johnson, 2001[12]. However, to accommodate various registration requirements in different countries, a full toxicity program for food enzymes has been performed

Toxicological data

(i) Metabolic and pharmacokinetic studies - Not applicable.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

The following studies have been conducted in accordance with internationally accepted guidelines (OECD/EU/FDA) and do not give any concerns:

- Acute oral toxicity in rats
- Bacterial reverse mutation – Ames assay
- In vitro mammalian chromosomal aberration test performed with human lymphocytes
- 13 – week oral (gavage) toxicity study in rats

The conclusion of the safety studies can be summarized as follows:

The safety of t transglucosidase/α-glucosidase is assessed in a battery of toxicology studies investigating its acute oral, genotoxic and systemic toxicity potential.

[12] Pariza MW, Johnson EA; Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century; Regul Toxicol Pharmacol 2001 Apr; 33 (2):173-86.

Transglucosidase/α-glucosidase is not hazardous based on acute oral study according to the classification scenario in the Directive of the Commission 93/21/EEC of April 27, 1993 and the Globally Harmonized System of Classification and Labeling of Chemicals (GHS), 2007. In genotoxicity studies transglucosidase/α-glucosidase is not mutagenic, clastogenic or aneugenic.

Daily administration of α transglucosidase/α-glucosidase by oral gavage for 18 consecutive weeks did not result in adverse systemic toxicity or adverse effects on clinical chemistry, hematology, functional observation tests and macroscopic and histopathologic examinations. Under the conditions of this assay, the NOAEL (no observed adverse effect level) is established at the highest dose tested, 63.64 mg total protein/kg bw/day corresponding to 74.8 mg TOS/kg bw/day or 3230 MTGU/kg bw/day.

(iii) Epidemiological and/or clinical studies and special considerations - Not applicable.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

The product conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing as prepared by the Joint FAO/WHO Expert Committee on Food Additives at its sixty-seventh meeting for publication in FAO JECFA Monographs 3 (2006) and to the acceptance criteria, impurity limits, other test and other requirements for enzyme preparations listed in the Food Chemicals Codex, 9th edition[13]

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

The transglucosidase/α-glucosidase enzyme preparation from *Trichoderma reesei* will be used as a processing aid in the production of iso-malto-oligosaccharides and in the manufacture of potable alcohol, lysine, lactic acid and MSG. It hydrolyses and transfers α-D-gluco-oligosaccarides resulting isomalto-oligosaccharides from malto-oligosaccharides and fermentable sugars from molasses. The enzyme will be deactivated or denatured by the several following steps in the processing such as distillation and carbon treatment under certain condition (pH and temperature). No enzyme will be present in the final product.

Transglucosidase/α-glucosidase is a protein and any residual amounts remaining in food consumed would have the same nutritional value accordingly. However, the use levels of transglucosidase/α-glucosidase are very low. As with other enzymes that are currently approved and used as processing aids, use of this product would have an insignificant impact on the nutritional value of the food.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used
Transglucosidase/α-glucosidase is intended for use as processing aid in the IMO production and in the manufacture of potable alcohol, lysine, lactic acid and MSG.

- IMO processing = 0.5 to 1.5 kg enzyme preparation/MT starch
- Potable alcohol processing = 6 to 20 gg enzyme preparation/MT starch
- Lysine processing = 4 kg enzyme preparation/MT starch
- Lactic acid processing = 4 kg enzyme preparation/MT starch
- MSG processing = 4 kg enzyme preparation/MT starch

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.
Under the worst case scenario, the cumulative daily exposure to transglucosidase/α-glucosidase from intake of syrup, potable alcohol, lactic acid, MSG and lysine is:

Syrup =	0.031 mg TOS/kg bw/day
Potable alcohol =	0.002 mg TOS/kg bw/day
Lactic acid =	0.008 mg TOS/kg bw/day
MSG =	0.059 mg TOS/kg bw/day
Lysine =	0.047 mg TOS/kg bw/day
Human Cumulative Exposure =	0.147 mg TOS/kg bw/day

Other information (as necessary/identified) - None

10 Date on which data could be submitted to JECFA - As soon as necessary.

[13] US Pharmacopeial. 2014 Enzyme preparations. Food Chemical Codex Edition 9, pp. 375-380. The United States Pharmacopeial Convention, Washington, DC.

PROPOSAL VI - Amyloglucosidase from *Talaromyces emersonii* expressed in *Aspergillus niger*

1. *Proposal for inclusion submitted by:* Danish Veterinary and Food Administration.

2. *Name of substance; trade name(s); chemical name(s):*

Substance: *Amyloglucosidase from* Talaromyces emersonii *expressed in* Aspergillus niger

Chemical name: Glucan 1,4-alpha-glucosidase; CAS 9032-08-0, EC 3.2.1.3

3. *Names and addresses of basic producers:* Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd Denmark

4. *Has the manufacturer made a commitment to provide data?*

Novozymes A/S commits to provide data to support the proposal for inclusion of the amyloglucosidase in the list of substances to be evaluated by JECFA.

5. *Identification of the manufacturer that will be providing data (Please indicate contact person):*

Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd
Denmark
Attn.: Peter Hvass phva@,novozymes.com
+45 4446 3610

6. Justification for use:

The amyloglucosidase enzyme preparation is used as a processing aid during food manufacture for hydrolysis of starch during processing of starch containing foods. The amyloglucosidase is typically used in the following food processes:

- Starch processing
- Beverage alcohol (distilling) processes
- Baking and other cereal based processes
- Brewing processes and other cereal based beverage processes
- Fruit and vegetable processing

7. Food products *and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):*

The enzyme preparation is not added to final foodstuffs but used as a processing aid during food manufacturing. The typical food processes in which the amyloglucosidase is used are listed in above section.

The amyloglucosidase is used at the minimum dosage necessary to achieve the desired enzymatic reaction. The ranges of dosage recommended for the amyloglucosidase are as follows (expressed in enzyme activity units):

Starch processing:

Up to 750 AGU per kilogram of starch dry matter.

Beverage alcohol (distilling) processes:

Up to 750 AGU per kilogram of starch dry matter.

Baking and other cereal based processes:

Up to 3500 AGU per kilogram of starch dry matter.

Brewing processes and other cereal based beverage processes:

Up to 4100 AGU per kilogram of starch dry matter.

Fruit and vegetable processing:

Up to 150 AGU per litre of juice. This corresponds to approximately 15000 AGU per kilogram of starch dry matter.

8. Is the compound currently used in food *that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in food in one or more country? (please identify the country(ies))*

The enzyme is marketed in a range of commercial products targeted for their applications, e.g. under the trade name of Saczyme which was approved in Denmark in 2009. The enzyme has also been positively evaluated by a number of regulatory authorities, resulting in inclusion on various positive lists, e.g. in France, Mexico, Brazil.

9. *List of data available (please check, if available)*

Toxicological data

(i) Metabolic and pharmacokinetic studies

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in

animals and genotoxicity studies

(iii) Epidemiological and/or clinical studies and special considerations

(iv) Other data

The following food toxicity program according to the EFSA Guideline[i] has been performed:

- Test for mutagenic activity (Ames Test)
- *In vitro* micronucleus
- 13 weeks oral toxicity study in rats

The main conclusions of the safety studies can be summarized as follows:

The amyloglucosidase preparation showed no mutagenic activity by testing in a bacterial reverse mutation assay (Ames Test) and did not induce micronuclei in cultured human peripheral blood lymphocytes in vitro.

The amyloglucosidase preparation did not result on treatment-related adverse effects when administered to rats for 13 weeks, and the overall No Observed Adverse Effect Level (NOAEL) is considered to be the highest administered dose, corresponding to 1470 mg TOS/kg body weight (bw)/day.

The safety studies described above were all performed on liquid amyloglucosidase enzyme concentrate produced in accordance with ordinary production procedure, omitting stabilization and standardization.

Aspergillus niger is generally considered to be a safe production organism with a long history of safe use for food ingredients. Furthermore, the production strain lacks the ability to produce relevant mycotoxins.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The amyloglucosidase enzyme preparation complies with the purity criteria recommended for enzyme preparations by Food Chemicals Codex (VIII online edition, 2012). In addition to this, the enzyme preparation also conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing (2006) as proposed by the Joint FAO/WHO Expert Committee on Food Additives in Combined Compendium of Food Additive Specifications.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

The exposure assessment is performed according to the Budget Method (ILSI, 1997). The Budget Method assumptions represent a "maximum worst case" situation of human consumption, in which the enzyme would be used at its maximum recommended dosages in all processed food and all processed beverages and not only in those food and drink processes described above.

Overall, the human exposure to the amyloglucosidase will be negligible because the enzyme preparation is used as a processing aid and in low dosages. It is also supposed that the totality of the food enzyme will end up in the final food. This assumption is exaggerated since the enzyme protein and the other substances resulting from the fermentation are diluted or removed in certain processing steps.

Therefore the safety margin calculation derived from this method is highly conservative.

Assumptions in the Budget Method

Solid food	The maximum energy intake over the course of a lifetime is 50 kcal/kg bw/day. 50 kcal corresponds to 25 g foods. Therefore, adults ingest 25 g foods per kg bw per day. Assuming that 50% of the food is processed food, the daily consumption will be 12.5 g processed foods per kg bw. It is further assumed that, in average, all processed food contains 25% starch (or starch-derived) dry matter = 3.12 g starch derived dry matter per kg bw per day.
Liquids	The maximum intake of liquids (other than milk) is 100 ml/kg bw/day. Assuming that 25% of the non-milk beverages is processed, the daily consumption will be 25 ml processed beverages per kg bw. It is further assumed that all processed beverages contain 10% starch hydrolysates = 2.50 g starch derived dry matter per kg bw per day. It is assumed that the densities of the beverages are ~ 1.

Theoretical Maximum Daily Intake (TMDI) calculation

Solid Food:

The highest dosage for solid food is 3500 AGU per kg starch based raw material. 3500 AGU correspond to 931 mg TOS. Based on this, 3.12 gram starch-derived dry matter in solid food will maximally contain 2.90 mg TOS.

Liquid Food:

The highest dosage for liquid food (excluding distilled beverage spirits vide supra) is 4100 AGU per kg starch based raw material. 4100 AGU corresponds to 1090 mg TOS. Based on this, 2.50 gram starch-derived dry matter in liquids will maximally contain 2.73 mg TOS.

The theoretical maximum daily intake (TMDI) of the enzyme by consumers is therefore:

2.90 + 2.73 = 5.63 mg TOS/kg body weight/day.

Other information as necessary

10. ***Date on which data could be submitted to JECFA:*** August 2016

[1] Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal (2009) 1305, 1-26

PROPOSAL VII - Beta-amylase from Bacillus flexus expressed in Bacillus licheniformis

1. Proposal for inclusion submitted by: Danish Veterinary and Food Administration.

2. Name of substance; trade name(s); chemical name(s)

Substance: Beta-amylase from Bacillus flexus expressed in Bacillus licheniformis

Chemical name: Beta-amylase; CAS 9000-91-3, EC 3.2.1.2

3. Names and addresses of basic producers: Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd Denmark

4. Has the manufacturer made a commitment to provide data?

Novozymes A/S commits to provide data to support the proposal for inclusion of the beta-amylase in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd
Denmark
Attn.: Peter Hvass
Email: phva@novozymes.com
Tel: +45 4446 3610

6. Justification for use:

The beta-amylase enzyme preparation is used as a processing aid during food manufacture for hydrolysis of starch, e.g. in order to obtain more consistent and efficient production of maltose syrups during processing of starch-containing foods.

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):

The enzyme preparation is not added to final foodstuffs but used as a processing aid during food manufacturing. The beta-amylase is used in processing of starch-containing foods.

The beta-amylase is used at the minimum dosage necessary to achieve the desired enzymatic reaction. The range of dosage recommended for the beta-amylase is up to 10000 BAMU per kg of starch dry matter.

8. Is the compound currently used in food that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in food in one or more country? (please identify the country(ies))

The enzyme is marketed under the trade name of Secura which was approved in Denmark in 2015. Novo-zymes has also applied for approval of the enzyme in France, Mexico and Brazil. The approvals are expected in 2016.

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

(iii) Epidemiological and/or clinical studies and special considerations

(iv) Other data

The following food toxicity program according to the EFSA Guidelinei has been performed:

- Test for mutagenic activity (Ames Test)
- In vitro micronucleus
- 13 weeks oral toxicity study in rats

The main conclusions of the safety studies can be summarized as follows:

The beta-amylase preparation showed no mutagenic activity by testing in a bacterial reverse mutation assay (Ames Test) and did not induce micronuclei in cultured human peripheral blood lymphocytes in vitro.

The beta-amylase preparation did not result in treatment-related adverse effects when administered to rats for 13 weeks, and the overall No Observed Adverse Effect Level (NOAEL) is considered to be the highest administered dose, corresponding to 1199 mg TOS/kg body weight (bw)/day.

The safety studies described above were all performed on liquid beta-amylase enzyme concentrate produced in accordance with ordinary production procedure, omitting stabilization and standardization.

Bacillus licheniformis is generally considered to be a safe production organism with a long history of safe use for food ingredients.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The beta-amylase enzyme preparation complies with the purity criteria recommended for enzyme preparations by Food Chemicals Codex (VIII online edition, 2012). In addition to this, the enzyme preparation also conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Pro-cessing (2006) as proposed by the Joint FAO/WHO Expert Committee on Food Additives in Combined Compendium of Food Additive Specifications.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

The exposure assessment is performed according to the Budget Method (ILSI, 1997). The Budget Method assumptions represent a "maximum worst case" situation of human consumption, in which the enzyme would be used at its maximum recommended dosages in all processed food and all processed beverages.

Overall, the human exposure to the beta-amylase will be negligible because the enzyme preparation is used as a processing aid and in low dosages. It is also supposed that the totality of the food enzyme will end up in the final food. This assumption is exaggerated since the enzyme protein and the other substances resulting from the fermentation are diluted or removed in certain processing steps.

Therefore the safety margin calculation derived from this method is highly conservative.

Budget Method

Assumptions in the

Solid food	The maximum energy intake over the course of a lifetime is 50 kcal/kg bw/day. 50 kcal corresponds to 25 g foods. Therefore, adults ingest 25 g foods per kg bw per day. Assuming that 50% of the food is processed food, the daily consumption will be 12.5 g processed foods per kg bw. It is further assumed that, in average, all processed food contains 25% starch (or starch-derived) dry matter = 3.12 g starch derived dry matter per kg bw per day.
Liquids	The maximum intake of liquids (other than milk) is 100 ml/kg bw/day. Assuming that 25% of the non-milk beverages is processed, the daily consumption will be 25 ml processed beverages per kg bw. It is further assumed that all processed beverages contain 10% starch hydrolysates = 2.50 g starch derived dry matter per kg bw per day. It is assumed that the densities of the beverages are ~ 1.

Theoretical Maximum Daily Intake (TMDI) calculation

Solid Food:

The highest dosage is 10000 BAMU per kilogram starch based raw material. 10000 BAMU correspond to 99.1 mg TOS. Based on this, 3.12 gram starch-derived dry matter in solid food will maximally contain 0.31 mg TOS.

Liquid Food:

The highest dosage is 10000 BAMU per kilogram starch based raw material. 10000 BAMU correspond to 99.1 mg TOS. Based on this, 2.50 gram starch-derived dry matter in liquids will maximally contain 0.25 mg TOS.

The theoretical maximum daily intake (TMDI) of the enzyme by consumers is therefore:

0.31 + 0.25 = 0.56 mg TOS/kg body weight/day.

Other information as necessary

10. Date on which data could be submitted to JECFA: August 2016

[1] Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Pro-cessing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal (2009) 1305, 1-26

PROPOSAL VIII - Lactase from *Bifidobacterium bifidum* expressed in *Bacillus licheniformis*

1. Proposal for inclusion submitted by: Danish Veterinary and Food Administration.

2. Name of substance; trade name(s); chemical name(s):

Substance: Lactase from *Bifidobacterium bifidum* expressed in *Bacillus licheniformis*

Chemical name: Beta-galactosidase; CAS 9031-11-2, EC 3.2.1.23

3. Names and addresses of basic producers: Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd Denmark

4. Has the manufacturer made a commitment to provide data?

Novozymes A/S commits to provide data to support the proposal for inclusion of the lactase in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd
Denmark
Attn.: Peter Hvass
E-mail: phva@novozymes.com
Tel: +45 4446 3610

6. Justification for use

The lactase enzyme preparation is used as a processing aid during food manufacture for hydrolysis of lactose during processing of milk and other lactose containing dairy products, e.g. in order to obtain lactose-reduced milk products for lactose-intolerant individuals as well as dairy products with better consistency and increased sweetness due hydrolysis of lactose to form glucose and galactose.

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):

The enzyme preparation is not added to final foodstuffs but used as a processing aid during food manufacturing. The lactase is used in processing of milk and other lactose containing food products.

The lactase is used at the minimum dosage necessary to achieve the desired enzymatic reaction. The range of dosage recommended for the lactase is up to 3500 LAU(B) per kg milk.

8. Is the compound currently used in food that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in food in one or more country? (please identify the country(ies))

A US GRAS (Generally Recognized As Safe) notification was submitted to FDA and the agency did not question Novozymes' conclusion that the lactase enzyme preparation is GRAS under the intended conditions of use. The enzyme was approved under the trade name NS46086 in Denmark in 2015. Novozymes has also applied for approval of the enzyme in France, Mexico and Brazil. The approvals are expected in 2016.

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

(iii) Epidemiological and/or clinical studies and special considerations

(iv) Other data

The following food toxicity program according to the EFSA Guidelinei has been performed:

- Test for mutagenic activity (Ames Test)
- In vitro micronucleus
- 13 weeks oral toxicity study in rats

The main conclusions of the safety studies can be summarized as follows:

The lactase preparation showed no mutagenic activity by testing in a bacterial reverse mutation assay (Ames Test) and did not induce micronuclei in cultured human peripheral blood lymphocytes in vitro.

The lactase preparation did not result in treatment-related adverse effects when administered to rats for 13 weeks, and the overall No Observed Adverse Effect Level (NOAEL) is considered to be the highest adminis¬tered dose, corresponding to 672 mg TOS/kg body weight/day.

The safety studies described above were all performed on liquid lactase enzyme concentrate produced in ac-cordance with ordinary production procedure, omitting stabilization and standardization.

Bacillus licheniformis is generally considered to be a safe production organism with a long history of safe use for food ingredients.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The lactase enzyme preparation complies with the purity criteria recommended for enzyme preparations by Food Chemicals Codex (VIII online edition, 2012). In addition to this, the enzyme preparation also conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing (2006) as proposed by the Joint FAO/WHO Expert Committee on Food Additives in Combined Compendium of Food Additive Specifications.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Method used for the dietary exposure assessment

Using EFSA Comprehensive European Food Consumption Database, the maximum average intake over 17 countries and all age groups, except infants, is 40.5 g "Milk and dairy products"/kg body weight/day.

Overall, the human exposure to the lactase will be negligible because the enzyme preparation is used as a processing aid and in low dosages. It is also supposed that the totality of the food enzyme will end up in the final food. This assumption is exaggerated since the enzyme protein and the other substances resulting from the fermentation are diluted or removed in certain processing steps.

Therefore the safety margin calculation derived from this method is highly conservative.

Theoretical Maximum Daily Intake (TMDI) calculation

The highest lactase dosage is 3500 LAU(B) per kg milk. 3500 LAU(B) correspond to 33.0 mg TOS. Based on this 40.5 g milk will maximally contain 1.34 mg TOS.

The theoretical maximum daily intake (TMDI) of the enzyme by consumers is therefore 1.34 mg TOS/kg body weight/day.

Other information as necessary

10. Date on which data could be submitted to JECFA: August 2016

i Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Pro¬cessing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal (2009) 1305, 1-26

PROPOSAL IX - Lipase from *Aspergillus oryzae* expressing a modified gene from *Thermomyces lanuginosus*

1. Proposal for inclusion submitted by: Danish Veterinary and Food Administration.

2. Name of substance; trade name(s); chemical name(s):

Substance: Lipase from *Aspergillus oryzae* expressing a modified gene from *Thermomyces la nuginosus*

Chemical name: Triacylglycerol lipase; CAS 9001-62-1, EC 3.1.1.3

3. Names and addresses of basic producers: Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd Denmark

4. Has the manufacturer made a commitment to provide data?

Novozymes A/S commits to provide data to support the proposal for inclusion of the lipase in the list of sub¬stances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Novozymes A/S Krogshøjvej 36 DK-2880 Bagsværd
Denmark
Attn: Peter Hvass
Email: phva@,novozymes.com
Tel: +45 4446 3610

6. Justification for use

The lipase enzyme preparation is used as a processing aid during food manufacture for hydrolysis of lipids during processing of lipid-containing foods, e.g. in order to improve dough strength and stability in baking and other cereal based processes.

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s)

The enzyme preparation is not added to final foodstuffs but used as a processing aid during food manufacturing. The lipase is used in baking and other cereal based food processes.

The lipase is used at the minimum dosage necessary to achieve the desired enzymatic reaction. The range of dosage recommended for the lipase is up to 2200 LU per kilogram flour.

8. Is the compound currently used in food that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in food in one or more country? (please identify the country(ies))

The enzyme is marketed under the trade name of Lipopan Xtra which was approved in Denmark in 2008. The enzyme has also been positively evaluated by a number of regulatory authorities, resulting in inclusion on various positive lists, e.g. in France, Mexico, Brazil.

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies;

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies;

(iii) Epidemiological and/or clinical studies and special considerations;

(iv) Other data

The following food toxicity program according to the EFSA Guideline has been performed:

- Test for mutagenic activity (Ames Test)
- In vitro micronucleus
- 13 weeks oral toxicity study in rats

The main conclusions of the safety studies can be summarized as follows:

The lipase preparation showed no mutagenic activity by testing in a bacterial reverse mutation assay (Ames Test) and did not induce micronuclei in cultured human peripheral blood lymphocytes in vitro.

The lipase preparation did not result in treatment-related adverse effects when administered to rats for 13 weeks, and the overall No Observed Adverse Effect Level (NOAEL) is considered to be the highest administered dose, corresponding to 1080 mg TOS/kg body weight (bw)/day.

The safety studies described above were all performed on liquid lipase enzyme concentrate produced in accordance with ordinary production procedure, omitting stabilization and standardization.

Aspergillus oryzae is generally considered to be a safe production organism with a long history of safe use for food ingredients. Furthermore, the production strain lacks the ability to produce relevant mycotoxins.

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

The lipase enzyme preparation complies with the purity criteria recommended for enzyme preparations by Food Chemicals Codex (VIII online edition, 2012). In addition to this, the enzyme preparation also conforms to the General Specifications and Considerations for Enzyme Preparations Used in Food Processing (2006) as proposed by the Joint FAO/WHO Expert Committee on Food Additives in Combined Compendium of Food Additive Specifications.

Intake assessment data

i. Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

ii. Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

The exposure assessment is performed according to the Budget Method (ILSI, 1997). The Budget Method assumptions represent a "maximum worst case" situation of human consumption, in which the enzyme would be used at its maximum recommended dosages in all processed food and not only in the baking and other cereal based food processes described above.

Overall, the human exposure to the lipase will be negligible because the enzyme preparation is used as a processing aid and in low dosages. It is also supposed that the totality of the food enzyme will end up in the final food. This assumption is exaggerated since the enzyme protein and the other substances resulting from the fermentation are diluted or removed in certain processing steps.

Therefore the safety margin calculation derived from this method is highly conservative.

Assumptions in the Budget Method

Solid food	The maximum energy intake over the course of a lifetime is 50 kcal/kg bw/day. 50 kcal corresponds to 25 g foods. Therefore, adults ingest 25 g foods per kg bw per day. Assuming that 50% of the food is processed food, the daily consumption will be 12.5 g processed foods per kg bw. Since the baking process on average results in 140 g of final baked product from 100 g of flour, it is further assumed that all processed food contains 70% flour = 8.75 g flour per kg bw per day.

Theoretical Maximum Daily Intake (TMDI) calculation

Solid Food:

The highest dosage is 2200 LU per kilogram flour. 2200 LU correspond to 20.05 mg TOS. Based on this, 8.75 gram flour based processed food will maximally contain 0.18 mg TOS.

The theoretical maximum daily intake (TMDI) of the enzyme by consumers is therefore 0.18 mg TOS/kg body weight/day.

***Other* information as necessary**

10. Date on which data could be submitted to JECFA: August 2016

[1] Guidance of EFSA prepared by the Scientific Panel of Food Contact Material, Enzymes, Flavourings and Processing Aids on the Submission of a Dossier on Food Enzymes. The EFSA Journal (2009) 1305, 1-26

PROPOSAL X - Basic Methacrylate Copolymer

Name of Substance(s):	**Basic Methacrylate Copolymer**
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation and establishment of specification when used as glazing / coating agent.

1. Proposal for inclusion submitted by:

Bundesministerium für Ernährung und Landwirtschaft (BMEL)
Federal Ministry of Food and Agriculture
Referat 311
(German Codex Contact Point)
Wilhelmstr. 54
10117 Berlin
Germany
Phone: +49-(0)30-18529-3515
E-Mail: codex.germany@bmel.bund.de

2. Name of substance; trade name(s); chemical name(s):

Name of substance: Basic Methacrylate Copolymer, INS 1205

Trade names: Eudraguard® protect

Chemical names: Poly(butyl methacrylate-co-(2-dimethylaminoethyl)methacrylate-comethyl methacrylate) 1:2:1, CAS number 24938-16-7

3. Names and addresses of basic producers:

Manufacturer:
Evonik Röhm GmbH
Kirschenallee
64293 Darmstadt
Germany

Marketer:
Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany

4. Has the manufacturer made a commitment to provide data?

Evonik Nutrition & Care GmbH commits to provide data to support the proposal for inclusion of Basic Methacrylate Copolymer in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany
Attn.: Dr. Uta Deiting, Regulatory Affairs Specialist Food
Email: uta.deiting@evonik.com ; Tel: +49 2407-5569960

6. Justification for use:

Glazing ageng / coating agent. „The technological function of the substance is to provide moisture protection and to mask the taste of various nutrients present in the treated products“ (EFSA opinion, p. 7, „*Summary*“)

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Food category: 13.6, food supplements
Max. use level: 100,000 mg/kg (10%)

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

EU: EU food additive list, (Reg. (EC) No. 1333/2008), Annex II: E 1205 (amendment for E 1205 by Reg. (EC) No 1129/2011). EFSA opinion attached.

US: GRAS status (according to Section 201(s) of the FDC Act): Self affirmed (June 2012), at a level of up to 10% by weight of the supplement. GRAS notice attached.

Other countries: product registration in progress / in preparation

9. List of data available (please check, if available)

Toxicological data

“Basic methacrylate copolymer is virtually not absorbed from the gastrointestinal tract after oral administration. This is in line with it being a stable high-molecular compound.”(EFSA opinion, p. 7, „*Summary*“)

The EFSA opinion on Basic Methacrylate Copolymer and the publication *Characterisation and toxicological behaviour of Basic Methacrylate Copolymer for GRAS evaluation* in the journal **Regulatory Toxicology and Pharmacology** ("RTP article"; both attached) provide details on the toxicological assessment.

(i) Metabolic and pharmacokinetic studies

See EFSA opinion, chapter 3.1, and RTP article, chapter 3.1. Quotation from EFSA opinion:

„An absorption, distribution, metabolism and excretion (ADME) study was performed with adult male rats (Charles River CD) in two phases. (…)

It was found that a mean total of 93.3% of the dose was eliminated via the faeces, mostly occurring within 48 hours after dosing. Similar values for recovery were obtained when faeces from untreated animals were spiked with the radiolabelled substance.

Excretion in urine was low, a mean total of 0.013% of the dose being excreted over the 5-day period following dosing. Although levels of radioactivity in urine were close to background levels, they were increased relative to controls 24 hours post-dose. This results in the conclusion that minor absorption from the gastro-intestinal tract may occur at less than 0.02%

of the administered dose. Analysis of blood and tissues indicate that no significant amount of any absorbed material was retained."

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

See EFSA opinion, chapter 3.2.2 – 3.2.5, and RTP article, chapter 3.2 – 3.4.

Selected quotations from the EFSA opinion:

- Short term toxicity

A study was conducted with Beagle dogs for 28 days. "The Panel notes that the study was conducted in compliance with GLP. The Panel noted that there is no OECD guideline for a 28-day oral toxicity study in dogs available, and that, according to the applicant, the OECD guidelines no.407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents) and no. 409 (Repeated Dose 90-Day Oral Toxicity Study in Non-Rodents) have been considered. (…)"

"The Panel considered 750 mg/kg bw/day, the highest dose tested, as the No-Observed-Adverse-Effect Level (NOAEL) as the few changes that were observed including the changes in body weight and food consumption following oral administration for a period of 28 days were not toxicologically relevant."

- Sub-chronic toxicity

A study was conducted with Sprague-Dawley rats for 26 weeks. "The petitioner points out that the study was carried out in 1973 when OECD and GLP guidelines were not yet implemented. However, the petitioner indicates that the study was undertaken by a recognised research organisation and the information available in the report indicates that the study was undertaken to standards generally in accordance with the requirements of OECD Test Guideline No.408. (…) The Panel considered that the NOAEL was 2000 mg/kg bw/day, the highest dose tested."

- Genotoxicity:

„Based on negative results derived from a gene mutation assay in *Salmonella typhimurium*, an *in vitro* mammalian cell gene mutation assay in L5178Y mouse lymphoma cells and an *in vivo* micronucleus assay, each performed according to current OECD guidelines and in compliance with GLP, the Panel concludes that basic methacrylate copolymer does not raise concern with respect to genotoxicity." (Source: chapter 4., Discussion)

- Chronic toxicity and carcinogenicity:

„No data were provided on chronic toxicity, however, given the high-molecular-weight of the substance and its lack of absorption, the EFSA panel considered that such data were not required." (Source: chapter 4., Discussion)

- Reproduction and developmental toxicity:

"There was no evidence of an effect of treatment on maternal animals."

"There were no effects on fetal survival as indicated by the extent of pre- and post-implantation loss (…) and the mean numbers of live fetuses (…). Fetal and placental weights were unaffected by treatment and so were the incidences and types of major fetal abnormalities. No treatment related effects were detected on the numbers of skeletal and visceral minor abnormalities and variants. The authors concluded the NOAEL for both dams and fetuses to be 1000 mg/kg bw/day."

"The petitioner did not provide data from studies on reproductive toxicity."

(iii) Epidemiological and/or clinical studies and special considerations

See EFSA opinion, chapter 3.2.6, and RTP article, chapter 3.6. Quotation from EFSA opinion:

No studies in humans have been provided. However, the petitioner indicates that the basic methacrylate copolymer is currently used as a pharmaceutical excipient and that, although it is widely used, no clinical trials have been specifically performed using the substance alone. The petitioner points out that basic methacrylate copolymer are a construct from methacrylate monomers. It is not a protein and has not been shown to form conjugates with endogenous proteins. The petitioner argues that the many years of use of the substance as an excipient in pharmaceutical preparations has not revealed immunotoxic effects in the human population. The petitioner therefore, considers that there is no concern regarding allergenicity."

The same is discussed a little bit more detailed in the RTP article.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

See EFSA opinion, chapters 2.1, Identity of substance, and 2.2., Specification, and commercial specification.

The product conforms to the specification as listed in Reg. (EU) No. 231/2012, with the exception of the particle size. The data named in the regulation were included there due to a misunderstanding. The correction of the particle size data is initiated at EFSA, see attached correspondence. The correct data are:

Particle size of powder: < 50 µm at least 95 %
< 20 µm at least 50 %
< 3 µm not more than 10 %

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

See below, intake assessment data.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

See EFSA opinion, chapter 2.6., Case of need and proposed uses. Quotation*:*

Basic methacrylate copolymer is intended to be used as a glazing agent/coating agent in solid food supplements as defined in European Parliament and Council Directive 2002/46/EC and in solid foods for special medical purposes as defined in Commission Directive 1999/21/EC. The use is therefore restricted to products in dosage form, namely forms such as capsules, pastilles, tablets, pills and other similar forms like pellets, and powders. (…)

The petitioner indicates that only low use levels for coating are needed and that taste masking and moisture protection can be achieved with coating levels of 1-5 mg basic methacrylate copolymer /cm2, equivalent to approximately 6 - 30 mg/tablet (for a tablet weight of 1000 mg). According to the petitioner the highest coating level could be up to 100 mg/ tablet (1000 mg)."

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

See EFSA opinion, chapter 2.8. (Quoted below), and RTP article, chapter 4.1., Exposure.

In the EFSA opinion, the exposure to basic methacrylate copolymer is extensively discussed. As a conclusion for use in food supplements, „the anticipated exposure to basic methacrylate copolymer would be 2 mg/kg bw/day and 3 mg/kg bw/day respectively for adults and approximately 2.4 mg/kg bw/day for children", based on a normal coating level of 30 mg/tablet. „Taking into account a tablet weight of 1000 mg and a highest coating amount up to 10% weight per unit, for a 60 kg adult this consumption would lead to an anticipated exposure to basic methacrylate copolymer of 6.7 mg/kg bw/day and 10.0 mg/kg bw/day, respectively for average and heavy users. For children, assuming a body weight of 25 kg, the potential exposure would be approximately 8 mg/kg bw/day.“

Furthermore, the petitioner also provided exposure estimates to basic methacrylate copolymer from use in pharmaceuticals. (…)The Panel assumed similar levels of use and intake of pharmaceutical products and supplements per day (EFSA, 2005). Given this assumption, the Panel estimated that the combined intake from food supplements and pharmaceutical products would be twice as high as the estimated intake for supplements only and would amount respectively to 16 mg/kg bw/day for children and to 23.3 mg/kg bw/day for adults (for a coating level of 100 mg methacrylic copolymer/tablet) and to 4.8 and 7.0 mg/kg bw/day, respectively (for a coating level of 30 mg methacrylic copolymer/tablet).“

Other information (as necessary/identified) - None

10. Date on which data could be submitted to JECFA: As soon as necessary.

Attachments:

1. BMC_Commercial specification_Eudraguard protect.pdf
2. BMC_EFSA opinion.pdf
3. BMC_EFSA request on particle size.pdf
4. BMC_Evonik reply on particle size.pdf
5. BMC_RTP article.pdf
6. BMC_GRAS notice.pdf

PROPOSAL XI - Neutral Methacrylate Copolymer

Name of Substance(s):	**Neutral Methacrylate Copolymer**
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation and establishment of specification when used as glazing / coating agent.

1. Proposal for inclusion submitted by

Bundesministerium für Ernährung und Landwirtschaft (BMEL)
Federal Ministry of Food and Agriculture
Referat 311
(German Codex Contact Point)
Wilhelmstr. 54
10117 Berlin
Germany
Phone: +49-(0)30-18529-3515
E-Mail: codex.germany@bmel.bund.de

2. Name of substance; trade name(s); chemical name(s)

Name of substance: Neutral Methacrylate Copolymer, INS 1206

Trade names: Eudraguard® control

Chemical names: Poly(ethylacrylate-co-methyl methacrylate) 2:1, CAS number 9010-88-2

3. Names and addresses of basic producers

Manufacturer	Marketer
Evonik Röhm GmbH Kirschenallee 64293 Darmstadt Germany	Evonik Nutrition & Care GmbH Kirschenallee 64293 Darmstadt Germany

4. Has the manufacturer made a commitment to provide data?

Evonik Nutrition & Care GmbH commits to provide data to support the proposal for inclusion of Neutral Methacrylate Copolymer in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany

Attn.: Dr. Uta Deiting, Regulatory Affairs Specialist Food

Email: uta.deiting@evonik.com; Tel: +49 2407-5569960

6. Justification for use

Glazing ageng / coating agent for sustained release formulations of nutrients in solid food supplements. Sustained-release formulations allows the continuous dissolution of a nutrient over a defined time.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s)

Food category: 13.6, food supplements
Max. use level: 200,000 mg/kg (20%)

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

EU: EU food additive list, (Reg. (EC) No. 1333/2008), Annex II: E 1206 (amendment for E 1206 by Reg. (EC) No 816/2013). EFSA opinion attached.

US: GRAS status (according to Section 201(s) of the FDC Act): Self affirmed (January 2014), at a level of max. 20 wt % in unit dosage. GRAS notice attached.

Other countries: product registration in progress / in preparation

9. List of data available (please check, if available)

Toxicological data

Neutral methacrylate copolymer is essentially not absorbed, and any absorbed material is not retained in the tissues. - The EFSA opinion on Neutral Methacrylate Copolymer and the publication *Characterisation and toxicological assessment of Neutral Methacrylate Copolymer for GRAS evaluation* in the journal **Regulatory Toxicology and Pharmacology** ("RTP article"; both attached) provide details on the toxicological assessment.

(i) Metabolic and pharmacokinetic studies

See EFSA opinion, chapter 3.1, and RTP article, chapter 3.1. Quotation from EFSA opinion:

An ADME study was performed with adult male rats (Charles River CD) in two phases. (…)

The major route of excretion was via the faeces. A mean total of 97.2% (range: 93.6-101.7%) of the dose was eliminated via this route, mostly occurring within the 48 hours following dosing. Urine showed very low levels of elimination (0.009% of the administered dose). Extremely low levels of radioactivity were recovered from the blood and a number of tissues, resulting in the conclusion that absorption from the gastro-intestinal tract was less than 0.02% of the administered dose. Analysis of blood and tissues did not indicate that significant amounts of any absorbed material were retained. From the data it can be concluded that the polymer is essentially not absorbed and that any absorbed material is not retained in the tissues.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

See EFSA opinion, chapter 3.2.2 – 3.2.5 and RTP article, chapter 3.2 – 3.4.

Selected quotations from the EFSA opinion (chapters named above or chapter 4., Discussion):

- Short term toxicity

No specific changes occurred during the study that were attributed to treatment and (…) the No-Observed-Adverse-Effect Level (NOAEL) identified in this study may be regarded as 2000 mg/kg bw/day, the highest dose tested (…). The Panel agrees with this NOAEL."

A study with minipigs was conducted in accordance with to EEC Council Directives 65/65 and 75/318 and subsequent amendments. "Following the 4 weeks of treatment, no toxicologically relevant changes were observed in body weight, food consumption, clinical observations, and clinical pathology investigations and in the organ weights. Histopathological examination revealed sporadic instances of mucosal / submucosal oedema in the caecum and colon of one male receiving 454 mg/kg bw/day and in the caecum of one male dosed at 227 mg/kg bw/day. According to the authors of the study, the effect of the high doses is unclear and the finding may be a physiological reaction of the intestine to the high amounts of non-soluble or non-degradable particles resulting in osmotic imbalance in this part of the intestine. According to the authors, no toxicological relevance could be attributed to this observation (Rossiello, 2006). The Panel agrees with this conclusion and identified a NOAEL of 454 mg/kg bw/day.

- Sub-chronic toxicity

„The results of the study show that the test substance, administered in the diet at dose levels up to 2000 mg/kg bw/day for 26 weeks was generally well tolerated. No treatment-related effects were noted on body weight, body weight gain, and food or water consumption. No clinical signs were apparent to indicate a treatment-related effect. Haematology and clinical chemistry parameters were not affected. No macroscopic or microscopic abnormalities were noted that were deemed to be a result of treatment. From the study the authors derived a NOAEL of 2000 mg/kg bw/day, the highest dose tested (…). The Panel agrees with this NOAEL."

"The petitioner provided also data of another 26 weeks study with Beagle dogs. (…) According to the authors, the lower body weights and the reduced food consumption observed at the highest dose tested, could be explained by the characteristics of the test substance and were not accompanied by any signs of toxicity to organs or tissues, a NOAEL of 250 mg neutral methacrylate copolymer/kg bw/day, the highest dose tested (…). The Panel agrees with this NOAEL."

- Genotoxicity:

„From the *in vitro* Ames and mammalian cell mutation assays and the micronucleus assay *in vivo*, the Panel considers that neutral methacrylate copolymer does not raise concern with respect to genotoxicity."

- Chronic toxicity and carcinogenicity:

„The Panel noted that the petitioner did not provide data on reproductive toxicity, chronic toxicity and carcinogenicity. In the absence of these data, chronic effects in the gastrointestinal tract following oral administration cannot be excluded. Therefore, the Panel considers that an ADI should not be established and that a margin of safety (MOS) approach is appropriate."

- Reproduction and developmental toxicity:

„The petitioner did not provide data from one or two generation reproductive toxicity studies. The petitioner provided data of two studies focussing on prenatal developmental toxicity. The Panel noted that the studies were carried out in 1974. The methods used were those described by the guidelines for reproductive studies for safety evaluation of drugs for human use of the FDA (1966) and the principles for the testing of drugs for teratogenicity, WHO, 1967. There were no indications that the studies were conducted in compliance with GLP. (…) The authors concluded the NOAEL for both dams and fetuses to be 2000 mg/kg bw/day. The Panel agrees with this NOAEL."

(iii) Epidemiological and/or clinical studies and special considerations

See EFSA opinion, chapter 3.2.6, and RTP article, chapter 3.6.

Quotation from EFSA opinion:

„No studies in humans have been provided. However, the petitioner indicates that the neutral methacrylate copolymer is currently used as a pharmaceutical excipient and that, although it is widely used, no clinical trials have been specifically performed using the substance alone".

Quotation from RTP article:

„Although it is widely used, no human volunteer studies or clinical trials have been specifically performed investigating the substance itself. The substance does, however, have a history of use as a pharmaceutical excipient in Europe, the USA and Japan. All these pharmaceutical preparations are subject to national and/or European pharmacovigilance systems. No adverse effects have ever been reported to the manufacturer from these systems with regard to the consumption of drugs formulated with NMC."

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

See EFSA opinion, chapters 2.1, Identity of substance, and 2.2., Specification, and commercial specification.

The product conforms to the specification as listed in Reg. (EU) No. 231/2012.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

See below, intake assessment data.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

See EFSA opinion, chapter 2.6., Case of need and proposed uses. Quotation:

"Neutral methacrylate copolymer is intended to be used as a sustained-release glazing agent/coating agent in solid food supplements. Sustained-release formulations allows the continuous dissolution of a nutrient over a defined time. Neutral methacrylate copolymer is insoluble in aqueous media over the complete pH range. The sustainedrelease functionality is obtained via the permeability of the coating for the nutrients in aqueous media. The addition of organic solvents is not necessary. The petitioner indicates that coating is done at temperatures in the range of 25 °C - 35 °C."

„The petitioner indicates that the amount of neutral methacrylate copolymer as glazing agent can be adjusted to the formulation to achieve sustained-release functionality. The sustained-release functionality can be achieved with a polymer amount of 10%. By increasing the polymer amount of the coating, the release profile can be modified to provide lower or higher release rates. It is indicated that the conventional polymer amount for a sustained-release profile is in the range of 10% to 20% (16.7 – 33.4 mg/cm²), equivalent to approximately 100-200 mg/tablet (for a tablet weight of 1000 mg)."

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

See EFSA opinion, chapter 2.8., and RTP article, chapter 4.1., Exposure. Quotation from EFSA opinion:

The petitioner provided an exposure assessment for (200 mg/tablet) using 2 supplements and 3 pharmaceutical pills per day for average user adults (3 supplements/day for heavy users) and 1 supplement and 1 pharmaceutical pill per day for children above 6 years. The total anticipated exposure from its combined use in solid food supplements and pharmaceutical pills of 200 mg/tablet would amount to either 16.7 mg/kg bw/day of neutral methacrylate copolymer for average adult users (i.e. 200 mg x 5 tablets), to 20 mg/kg bw/day for heavy adult users (i.e. 200 mg x 6 tablets), and to 16 mg/kg bw/day for children (i.e. 200 mg x 2 tablets), respectively. The Panel noted that the estimates provided by the petitioner are (slightly) lower than the estimates made on assumptions used by the Panel in previous evaluations (EFSA, 2004; EFSA, 2005). Data from the UK Food Standard Agency on the consumption of food supplements indicate that the use among high consumers (97.5th percentile) ranged from 2 tablets/capsules per day in young people (4-18 years) (Gregory, 2000) to 7 tablets/capsules per day in adults (Henderson et al., 2002). Therefore, the Panel calculated an anticipated exposure to neutral methacrylate copolymer (see Table 2) from its combined use in solid food supplements and pharmaceutical pills of 46.7 mg/kg bw/day of neutral methacrylate copolymer for high adult consumers (based on a coating of 200 mg/tablet) and of 32 mg/kg bw/day for children, respectively. Assuming a coating level of 200 mg methacrylate copolymer per tablet, the anticipated total exposure for high consumers resulted in 2800 mg/day (200 mg x 14 tablets) and 800 mg/day (200 mg x 4 tablets) of neutral methacrylate copolymer for adults and children, respectively."

Other information (as necessary/identified) - None

10. Date on which data could be submitted to JECFA - As soon as necessary.

Attachments:

1. NMC_Commercial specification_Eudraguard control.pdf
2. NMC_EFSA opinion.pdf
3. NMC_RTP article.pdf
4. NMC_GRAS notice.pdf

PROPOSAL XII - Anionic Methacrylate Copolymer

Name of Substance(s):	**Anionic Methacrylate Copolymer**
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation and establishment of specification when used as glazing / coating agent.

1. Proposal for inclusion submitted by:

Bundesministerium für Ernährung und Landwirtschaft (BMEL)
Federal Ministry of Food and Agriculture
Referat 311
(German Codex Contact Point)
Wilhelmstr. 54
10117 Berlin
Germany

Phone: +49-(0)30-18529-3515
E-Mail: codex.germany@bmel.bund.de

2. Name of substance; trade name(s); chemical name(s):

Name of substance: Anionic Methacrylate Copolymer, INS 1207

Trade names: Eudraguard® biotic

Chemical names: Poly (methyl acrylate-co-methylmethacrylate-co-methacrylic acid) 7:3:1, CAS number 26936-24-3

3. Names and addresses of basic producers:

Manufacturer:

Evonik Röhm GmbH
Kirschenallee
64293 Darmstadt
Germany

Marketer:

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany

4. Has the manufacturer made a commitment to provide data?

Evonik Nutrition & Care GmbH commits to provide data to support the proposal for inclusion of Anionic Methacrylate Copolymer in the list of substances to be evaluated by JECFA.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Evonik Nutrition & Care GmbH
Kirschenallee
64293 Darmstadt
Germany
Attn.: Dr. Uta Deiting, Regulatory Affairs Specialist Food
Email: uta.deiting@evonik.com Tel:+49 2407-5569960

6. Justification for use:

Quotation from EFSA opinion (p. 7, „*Background as provided by The European Commission*"):

"Enteric coating in the production of formulations of solid food supplements. The enteric properties of glazing agents protect the stomach against irritating nutraceutical ingredients. On the other hand, sensitive nutrients are protected against disintegration by the stomach acid. (…) The consumer can benefit from the better compatibility of the nutraceutical ingredients; the compliance with the intake recommendations can be facilitated, the amount of nutrient can be better managed and the safety of the food supplement can be improved."

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Food category: 13.6, food supplements
Max. use level: 100,000 mg/kg (10%)

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies))

EU: EU food additive list, (Reg. (EC) No. 1333/2008), Annex II: E 1207 (amendment for E 1207 by Reg. (EC) No 816/2013). EFSA opinion attached.

US: GRAS status in preparation

Other countries: product registration in progress / in preparation

9. List of data available (please check, if available)

Toxicological data

Anionic methacrylate copolymer is very poorly absorbed from the gastrointestinal tract. It is predominantly excreted via the faeces following transit through the gastrointestinal tract. From the data using radiolabelled anionic methacrylate copolymer it can be concluded that the polymer is essentially not absorbed and that the very low amounts of absorbed radioactivity are not retained in the tissues. – The EFSA opinion on Anionic Methacrylate Copolymer provide details on the toxicological assessment.

(i) Metabolic and pharmacokinetic studies

See EFSA opinion, chapter 3.1. Quotation:

„The petitioner provided data of an ADME study performed according to Good Laboratory Practices. The

ADME study was performed with male and female rats (CD Sprague-Dawley strain). (…)

„The study shows that, following ingestion, anionic methacrylate copolymer is very poorly absorbed from the gastrointestinal tract. It is predominantly excreted via the feces following transit through the gastrointestinal tract (Jolly,

1999). The petitioner argues that the very low level of absorption prevents the investigation of the kinetics of absorption/elimination and the determination of possible metabolism. However, the Panel does not preclude the existence of gastrointestinal metabolism."

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

See EFSA opinion, chapter 3.2.2 – 3.2.5. Selected quotations:

- Short term toxicity

The petitioner provided data from a 28-day study in the dog. The Panel noted that the study was performed according to GLP. (…) The authors concluded the No-Observed-Adverse-Effect Level (NOAEL) to be 400 mg/kg bw/day, the highest dose tested (Eileraas, 2004). The Panel agrees with this NOAEL.

- Sub-chronic toxicity

The petitioner provided data from a 26-week oral toxicity study in the rat. The Panel noted that the study was performed according to GLP. (…) The authors derived a NOAEL of 1500 mg/kg bw/day, the highest dose tested (Venturella, 2000). The Panel agrees with this NOAEL.

- Genotoxicity

Based on negative results derived from the in vitro Ames and mammalian cell mutation assays and the micronucleus assay in vivo, the Panel considers that anionic methacrylate copolymer does not raise concern with respect to genotoxicity.

- Chronic toxicity and carcinogenicity

No data were provided.

- Reproduction and developmental toxicity

The petitioner did not provide data from one or two generation reproductive toxicity studies. – The petitioner provided data from a study assessing the effects of anionic methacrylate copolymer (AMC) on the survival and development of the unborn fetuses when administered during the organogenesis phase of gestation and until the completion of fetal development in the pregnant rats (Schmidt, 2003). The study was conducted in accordance with OECD guideline for the testing of chemicals No. 414. (…) The NOAEL for both dams and fetuses is 1000 mg/kg bw/day.

(iii) Epidemiological and/or clinical studies and special considerations

See EFSA opinion, chapter 3.2.6. Quotation:

The petitioner states that no human volunteer studies have been undertaken with anionic methacrylate copolymer. The material has a limited history of use as a pharmaceutical excipient although analogous copolymers have an extensive history of such use with no reported adverse effects.

(iv) Other data - None.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

See EFSA opinion, chapters 2.1, Identity of substance, and 2.2., Specification, and commercial specification.

The product conforms to the specification as listed in Reg. (EU) No. 231/2012.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

See below, intake assessment data.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

See EFSA opinion, chapter 2.6., Case of need and proposed uses. Quotation:

Anionic methacrylate copolymer is intended to be used as a glazing agent/coating agent in solid food supplements. The use is therefore restricted to products in dosage form, namely forms such as capsules, pastilles, tablets, pills and other similar forms like pellets, and powders. The petitioner states that anionic methacrylate copolymer will be specifically used for its 'enteric' properties, i.e. to protect the stomach against irritating ingredients (e.g. iron ions) or to protect sensitive nutrients against disintegration by the gastric acid.

The petitioner indicated that only low use levels for coating are needed since the enteric properties can be obtained with a coating level of 5 mg/cm2, equivalent to 30 mg/tablet (tablet weight: 1000 mg). For special applications, higher coating levels are necessary. The highest coating level is estimated to be 100 mg/ tablet.

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

See EFSA opinion, chapter 2.8.. Quotation from chapter 4.Discussion:

As regards exposure, the Panel based its estimate on the worst case combined exposure by heavy users (assuming a coating level of 100 mg/tablet) to anionic methacrylate copolymer from both its proposed use in food supplements and from its approved use in pharmaceuticals, estimated to be equal to 23.4 mg/kg bw/day for a 60 kg adult, and 16 mg/kg bw/day for children (4-18 years), whereas the petitioner estimated this exposure to be 20 mg/kg bw/day and 16 mg/kg bw/day respectively. The Panel estimated the combined exposure to anionic methacrylate copolymer for heavy users assuming the normal maximum coating level of 30 mg/tablet, from both its proposed use in food supplements and from its approved use in pharmaceuticals to be 7 mg/kg bw/day for a 60 kg adult, and 4.8 mg/kg bw/day for a child. The respective estimates by the petitioner for these user groups are 6 mg/kg bw/day and 4.8 mg/kg bw/day. If anionic methacrylate is used solely in food supplements at the normal coating level of 30 mg/tablet, the estimated exposure by heavy users would be 3.5 mg/kg bw/day for adults and 2.4 mg/kg bw/day for children. Using the worst case exposure, the calculated exposure to the residual monomers (methacrylic acid, methyl acrylate and methyl methacrylate) present in the substance would be less than 0.76 µg/kg bw/day (expressed as methacrylic acid) for adults, and less than 0.54 µg/kg bw/day (expressed as methacrylic acid) for children. The Panel noted that these figures are far below the group Tolerable Daily Intake (TDI) of 0.1 mg/kg bw/day (expressed as methacrylic acid) for these monomers as established by the SCF.

The NOAELs derived from the available studies are: 1000 mg/kg bw/day from a developmental study in the rat (single dose level tested) and 1500 mg/kg bw/day from a 26-week feeding study in the rat (highest dose tested). Using this range of NOAELs and assuming the highest coating level (100 mg/tablet) and a combined exposure from food supplements and pharmaceuticals of 23.4 mg/kg bw/day for a 60 kg adult, and 16 mg/kg bw/day for children (4-18 years), the Panel calculates a margin of safety (MOS) for heavy users varying from at least 43 to 64 for adults and from 63 to 94 for children. If only the exposure from food supplements is considered, the MOS ranges from 85 to 128 for adults and from 125 to 188 for children. Given the high molecular weight of the substance, its lack of absorption, the fact that the MOS values are based on NOAELs that were the highest dose levels tested and that the exposures estimates were worst case, the Panel considers these MOS values sufficient.

Other information (as necessary/identified) - None

10. Date on which data could be submitted to JECFA - As soon as necessary.

Attachments:

1. AMC_Commercial specification_Eudraguard biotic.pdf
2. AMC_EFSA opinion.pdf

JAPAN

PROPOSAL 1 - Sucrose esters of fatty acids (INS 473)

Name of Substance(s):	Sucrose esters of fatty acids (INS 473)
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Revision of specifications (Change the statements for solubility in Identification)

1. Proposal for inclusion submitted by: JAPAN

2. Name of substance; trade name(s); chemical name(s): Sucrose esters of fatty acids (INS 473)

3. Names and addresses of basic producers:

(i) Mitsubishi Chemical Corporation, 1-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo 100-8251, Japan

(ii) Dai-ichi Kogyo Seiyaku Co.,Ltd, 5 Ogawara-cho, Kisshoin, Minami-ku, Kyoto 601-8391, Japan

4. Has the manufacturer made a commitment to provide data? Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Mitsubishi Chemical Corporation
Scientific Regulatory Affairs Manager
Food Ingredients Department
Performance Product Division
Ms. Yukino Nagai
Email: nagai.yukino@me.m-kagaku.co.jp

6. Justification for use: Used in various foods as an emulsifier and a stabilizer

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s): See the Attachment-1

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies)):

Yes. Sucrose esters of fatty acids is approved and used in foods in Japan, the USA, the EU, Australia and New Zealand, China, Korea, Taiwan, Vietnam, Philippines, Indonesia, Malaysia, Singapore, India and many other countries.

9. List of data available (please check, if available)

Toxicological and Intake estimate data; An ADI for Sucrose esters of fatty acids together with Sucroglycerides, Sucrose oligoesters Type I and Type II, and Sucrose monoesters of lauric, palmitic or stearic acid was established at the 73rd JECFA(2010).

Technological data; Sucrose esters of fatty acids (INS 473; SEFA) are consisted of mono-, di- and tri-esters of sucrose with fatty acids, and the assay is not less than 80% of sucrose esters. Hydrophilicity of this food additive depends both on fatty acid type and the content of monoesters.

We investigated the solubility of globally marketed products and the results are shown in Table 1. Some samples did not meet current solubility specification (Note; those products met all specifications except for solubility). Especially samples 4 and 6, of which the safety was evaluated by JECFA and which are major products currently used as a food additive around the world, did not meet solubility specification in water and ethanol.

Based on the results of the investigation, we would like to propose revisions of the solubility as follows: “Soluble, sparingly soluble or dispersible in warm water. Soluble in warm ethanol.”

Table 1. Results of solubility test of SEFA samples with current specification and proposing specification

SEFA Sample	Fatty acid type	ester composition		current spacification		proposing specification	
		Monoester (%)	Di and higher esters(%)	Water (20 ° C)	Ethanol (20 ° C)	Water (60° C)	Ethanol(50 ° C)
				Sparlingly soluble	Soluble	Soluble, sparlingly soluble or dispersible	Soluble
1	C12 (lauric)	ca. 80	ca. 20	Pass	Pass	Pass (soluble)	Pass
2	C16 (palmitic)	ca. 80	ca. 20	Not pass	Pass	Pass (sparlingly soluble)	Pass
3	C18 (stearic)	ca. 75	ca. 25	Not pass	Pass	Pass (sparlingly soluble)	Pass
4*	C18 (stearic)	ca. 55	ca. 45	Not pass	Not pass	Pass (dispersible)	Pass
5	C12 (lauric)	ca. 30	ca. 70	Not pass	Pass	Pass (dispersible)	Pass
6*	C18 (stearic)	ca. 30	ca. 70	Not pass	Not pass	Pass (dispersible)	Pass

Samples 4* and 6* are products of which the safety was evaluated by JECFA, and are major products used as a food additive around the world.

10. Date on which data could be submitted to JECFA: Immediately

PROPOSAL 2 - β-Glucanase from *Streptomyces violaceoruber* expressed in *S. violaceoruber*

Name of Substance(s):	**β-Glucanase from *Streptomyces violaceoruber* expressed in *S. violaceoruber***
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid and establishment of specifications

1. Proposal for inclusion submitted by: JAPAN

2. Name of substance; trade name(s); chemical name(s):

Name of substance: Glucanase from *Streptomyces violaceoruber* expressd in *S. violaceoruber*

Trade names: DENAZYME GEL-L1 or DENAZYME GEL-P1

Chemical name: 3-beta-D-glucan glucanohydrolase (EC 3.2.1.39)

3. Names and addresses of basic producers:

Nagase ChemteX Corporation
1-52, Osadanocho, Fukuchiyama,
Kyoto, 620-0853, Japan
(Attn: Mr Taku Fujimoto, General Manager Biochemicals department)
Tel: +81-773-27-5801
Fax:+81-773-27-2040
e-mail: taku.fujimoto@nagase.co.jp

4. Has the manufacturer made a commitment to provide data? - Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Nagase ChemteX Corporation
1-52, Osadanocho, Fukuchiyama,
Kyoto, 620-0853, Japan
(Attn: Mr Kensaku Uzura, Quality Assurance Section 3)
Tel: +81-773-27-5803
Fax:+81-773-27-2040
e-mail : kensaku.uzura@ncx.nagase.co.jp

6. Justification for use:

The glucanase preparation is used in the production of yeast extract, which is used as the key ingredient in seasonings, soups, sauces and gravies. The enzyme preparation disrupts the yeast cell wall, leading to increase in yield volume of yeast extract and improve residual filtration by hydrolysing β-D-glucan.

The benefit of the use of industrial glucanase is the reduction of bacterial contamination during yeast extract manufacturing. In addition, a longer reaction time results in reducing the amount of glucanase used which in turn decreases the manufacturing cost.

In general, the glucanase does not exert any (unintentional) enzymatic activity in the final food and only acts on D-glucans that are normal constituents of foodstuffs. No effect can occur on other food constituents such as proteins and lipids

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

The food category within the GSFA is; Yeast and like products (Food Category 12.8).

The ranges of the use levels of Glucanase ranges (mg TOS / kg food) can be provided. (An example is indicated in "Intake assessment data" section.

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies))

Currently, this glucanase preparation is only approved in Japan. In Europe and USA, the dossier is under evaluation

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies - Not applicable

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

This glucanase preparation has been subjected to toxicological tests as follows:

a) Ames test (Test for mutagenic activity)

b) Chromosomal aberrations

c) Micronucleus Test

d) Acute Toxicity Test on rats

e) 90-day oral toxicity on rats

(iii) Epidemiological and/or clinical studies and special considerations - Not applicable

(iv) Other data - None

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

Its specifications comply with "General Specifications and Considerations for Enzyme Preparations used in Food Processing"

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

The enzyme preparation is used in the production of yeast extract, which is used as the key ingredient in seasonings, soups, sauces and gravies.

The enzyme preparation disrupts the yeast cell wall, leading to increase in yield volume of yeast extract and improve residual filtration by hydrolysing β-D-glucan. During sterilization step of making yeast extract, the enzyme is inactivated and no residual enzyme activity remains in the final product. In general, the glucanase does not exert any (unintentional) enzymatic activity in the final food and only acts on D-glucans that are normal constituents of foodstuffs. No effect can occur on other food constituents such as proteins and lipids. Thus the use of the enzyme preparation has no influence on the nutritional properties of final food.

The benefit of the use of industrial glucanase is the reduction of bacterial contamination during yeast extract manufacturing. In addition, a longer reaction time results in reducing the amount of glucanase used which in turn decreases the manufacturing cost.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

The enzyme preparation is intended to use in the manufacturing of yeast extract, which can be used as ingredient mainly

in seasonings. The intended use levels are:

- 0.3% of powdered glucanase preparation or 151.00 mg TOS/kg food;
- 0.6% of liquid glucanase preparation or 202.00 mg TOS/kg food.

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Using the most recommended Budget method, the Theoretical Maximum Daily Intake (TMDI) is estimated as 6.31 mg TOS/kg body weight/day for the general population.

Other food intake estimates were performed for each consumer category using the EU Datex database considering only the category "Seasoning or extracts".

These calculations give maximum intakes of the enzyme preparation by children as 46.9 and 266.1 µg TOS/kg body weight/day at the mean and the 97.5 percentile, respectively.

However, it must be emphasized that these food exposures are based on conservative assumptions and represent a highly exaggerated value based on following assumptions:

- It is assumed that ALL food producers use the food enzyme at the highest recommended level
- It is assumed that consumers only eat foodstuffs processed with the enzyme preparation (aggregated/cumulative exposures).
- For the estimates using the Datex database, it is assumed that people intakes are the maximum available in these databases.

Other information (as necessary/identified)- None

10: Date on which data could be submitted to JECFA - Immediately

PROPOSAL 3 - Phospholipase A2 from *Streptomyces violaceoruber* expressed in *S. violaceoruber*

Name of Substance(s):	**phospholipase A2 from *Streptomyces violaceoruber* expressed in *S. violaceoruber***
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation when used as processing aid and establishment of specifications

1. Proposal for inclusion submitted by: JAPAN

2. Name of substance; trade name(s); chemical name(s):

Name of substance: phospholipase A2 from *Streptomyces violaceoruber* expressed in *S. violaceoruber*

Trade names: PLA2 Nagase or PLA2 Nagase 10P

Chemical name: phosphatidylcholine-2-acylhydrolase (EC 3.1.1.4)

3. Names and addresses of basic producers:

Nagase ChemteX Corporation
1-52, Osadanocho, Fukuchiyama,
Kyoto, 620-0853, Japan
(Attn: Mr Taku Fujimoto, General Manager Biochemicals department)
Tel: +81-773-27-5801
Fax: +81-773-27-2040
e-mail: taku.fujimoto@nagase.co.jp

4. Has the manufacturer made a commitment to provide data? - Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Nagase ChemteX Corporation
1-52, Osadanocho, Fukuchiyama,
Kyoto, 620-0853, Japan
(Attn: Mr Kensaku Uzura, Quality Assurance section 3)
Tel: +81-773-27-5803
Fax: +81-773-27-2040
e-mail : kensaku.uzura@ncx.nagase.co.jp

6. Justification for use:

The enzyme preparation is used in the production of modified egg yolk and modified lecithin, both of which can be used as emulsifying agents (for example in chocolate, mayonnaise, tamagoyaki etc.).

It is also used in the hydrolysis of triglycerides and phospholipids in cereal flour and dairy products. The enzyme preparation helps to improve emulsification properties of modified lipids increasing yield and texture of the final food in dairy and bakery.

In addition, the enzyme preparation can also be used for degumming of vegetable oil.

The benefit of using enzyme in the degumming process are as follows;

Cost reduction by improving production yield and reducing water consumption in the process.

To be improved into an Eco-Friendly process by using enzyme instead of chemicals.

The main benefits of the phospholipase A2 preparation in food production are:

- Better and/or more consistent product quality
- Effective food production processes, resulting in responsible use of food resources by reducing loss or waste of food materials.

In general, the phospholipase A2 does not exert any (unintentional) enzymatic activity in the final food. No effect can occur on other food constituents such as proteins and hydrocarbons. As no subsidiary activities are measured in the preparation, no other unintended effects could happen in the final food.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

The food categories within the GSFA are; Cream (FC 01.4), Cheese (FC 01.6), Dairy based desserts (FC 01.7), Vegetable oils and fats (FC 02.1.2), Pastas and noodles like products (FC 06.4), Bakery wares (FC 07.0), Egg and egg products (FC 10.0).

The ranges of the use levels of PLA2 ranges (mg TOS / kg food) can be provided. (Some examples are indicated in the table in “Intake assessment data” section.

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies))

Currently, this phospholipase A2 preparation is approved in Japan, USA, Canada, France, and Australia - New Zealand for number of food applications.

9. List of data available (please check, if available)

Toxicological data

i. Metabolic and pharmacokinetic studies - Not applicable

ii. Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

This phospholipase A2 preparation has been subjected to toxicological tests as follows:

a) Ames test (Test for mutagenic activity)

b) Chromosomal aberrations

c) Acute Toxicity Test on rats

d) 90-day oral toxicity on rats

iii. Epidemiological and/or clinical studies and special considerations - Not applicable

iv. Other data - None

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

Its specifications comply with the French Arrêté from 2006 and with “General Specifications and Considerations for Enzyme Preparations used in Food Processing”

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

The enzyme preparation is used in the production of modified egg yolk, modified lecithin and in the preparation of Tamagoyaki (Japanese rolled omelet). It is also used in the hydrolysis of triglycerides and phospholipids in cereal flour and dairy products. In addition, vegetable oil degumming can be performed using the enzyme preparation.

The use of enzyme preparation helps in emulsification to improve texture and yield in bakery and dairy products.The main benefits of the phospholipase A2 preparation in food production are:

- Better and/or more consistent product quality
- Effective food production processes, resulting in responsible use of food resources by reducing loss or waste of food materials

During food processing, the enzyme is inactivated or denatured due to combination of various conditions such as depletion of substrate, lack of water activity, extreme pH-temperature conditions. As a result, no residual enzyme activity remains in the final product. Thus the use of the enzyme preparation has no influence on the nutritional properties of final food.

Intake assessment data

(iii) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

This enzyme preparation is intended to use in the production of egg yolks, flour, vegetable oil and dairy products.

Food enzyme preparations are used by food manufacturers according to the *Quantum Satis* principle, which means that food manufacturers will typically fine-tune the enzyme dosage based on a dose range recommended by Nagase.

The table below provides the recommended maximum levels of use of the PLA2 preparation.

Requested maximum use levels of the PLA2 preparations

Foodstuff / ingredient	**Powder PLA2 preparation (mg TOS/kg)**	**Liquid PLA2 preparation (mg TOS/kg)**
egg yolks	21.04	91.73
flour	0.63	2.75
vegetable oils	0.63	2.75
dairy products	2.10	9.17

(iv) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Using the most recommended Budget method, the Theoretical Maximum Daily Intake (TMDI) is estimated as 0.066 and 0.287 mg TOS/kg body weight/day for PLA2 powder and PLA2 liquid respectively.

Other food intake estimates were performed using the EU Datex database and considering the corresponding categories. These calculations give maximum dietary exposures for the “other children” category of:

- 287.1 µg TOS/kg BW/day at the 97.5 percentile for the liquid preparation
- 65.9 µg TOS/kg BW/day at the 97.5 percentile for the solid preparation

However, it must be emphasized that these food exposures are based on conservative assumptions and represent a highly exaggerated values based on following assumptions:

- It is assumed that ALL food producers use the food enzyme at the highest recommended level.
- It is assumed that consumers only eat foodstuffs processed with the enzyme preparation (aggregated/cumulative exposures).
- For the estimates using the Datex database, it is assumed that people intake s are the maximum available in these databases.

Other information (as necessary/identified) - None

10. Date on which data could be submitted to JECFA – Immediately

SUDAN

First, Gum Arabic in the priority list was mentioned without the INS no. E414, which indicates that Gum Arabic has been considered as a new substance as referred to in CCFA report at the 47th Session of CCFA. Therefore, Sudan will appreciate a clarification of the situation.

Gum Arabic is dried exudates obtained from stems and branches of *Acacia senegal* trees which are cultivated in the Sudan as a cash crop in agro forestry systems (Duke1981). The international specifications used to assess the quality of gum arabic in the world market are based on the Sudan gum obtained from *A. senegal* variety *senega*l (Beshai, 1984; Larson and Bromley, 1991; Macrae and Merlin, 2002). The international specifications of quality parameters of gum arabic(*Acacia senegal*) are given in Table 1.

Table 1. International specifications of quality parameters of gum arabic*.

Property	**Range**
Moisture content (%)	13 - 15
Ash content (%)	2 - 4
Internal energy (%)	30 - 39
Volatile matter (%)	51 - 65
Optical rotation (degrees)	-26 - -34
Nitrogen content (%)	0.26 - 0.39

Cationic composition of total ash (550° C)

Copper (ppm) Iron (ppm) Manganese (ppm) Zinc (ppm)

52 - 66 730– 249069 - 117 45 - 111

Source of Gum arabic: Kordofan gum belt region, Sudan. Species: A. senegal var. Senegal and its varieties. *Ref: FAO (1990).

Gum Arabic(A. Senegal) is a natural organic dried exudates produced from the trunk and branches of the A. senegal tree, known as "hashab" or hard gum, and the (Gum Talha) A. seyal tree, known as "Taleh" or flaky gum [12]. The gum is a pale white to orange brown solid which breaks with a glassy fracture, and is widely used in the food and pharma-ceutical industry as an emulsifier, stabilizer, texturizer, film former and binder. "Acacia gum" as an item of trade dates back to the 17th century B.C. when it was traded by Arab traders who bought the gum from Sahelian West and Central Africa to Egypt and Europe. Sudan is primarily the world's largest producer of gum Arabic; it contributes to about 95% of the total world gum Arabic production [13]. Sudan effectively controls almost over 80% of the world market [13]-[15]. Gum Arabic provides an average of 12% of the gross domestic product (GDP) of the country. Gum production ac-counts for about 15.3% and 10% of the household income of gum producers and other farmers in the gum belt in Sudan, respectively [16] [17]. It was ascertained that gum production was economically more efficient and much less labor intensive compared to all other alternative cash crops [17]. As well, it was verified that gum Arabic as a product of small household farm system has a good comparative advantage and relatively higher international competitiveness in relation to other competing cash crops [16]. Gum production is characterized by a remarkable flexibility as a means for combating poverty as it provides insurance service against risks and uncertainties.

Quality, quantity, availability and economics are the key factors that affect the marketing of any product, irrespective of whether it is for domestic, national or international market. The consumer requires the product to be available in time, be of desired quality and quantity. The market of gum arabic is a good example of how the interplay of quality, quantity, availability and economics affect a product market.

The majority of the populations in the gum Arabic producing areas in Sudan rely heavily on traditional agriculture, livestock and range activities due to their considerable contribution to the household food security therefore enhances soil stabilization and soil fertility through biological nitrogen fixation thus contributing to the environmental conservation (Wickens et al., 1996). The tree provides grazing and browsing material for livestock. Thus, Gum Arabic (A. Senegal) can provide a potential solution to land degradation in the ASALs. Moreover, its promotion and utilization can offer alternative livelihoods to the pastoralists and agro-pastoralists contribute to soil fertility and protect these fragile ecosystems from environmental degradation.

The major determinant of the production of any industrial crop is its demand and the revenue derivable from it. That is, the better the market situation of a crop for higher production among farmers, Sudan effectively controls about 85% of the World Market, with the West African countries Senegal, Mauritania, Mali, Chad, Niger and Nigeria supplying much of the remainder (Anderson, 1993).

Studies show that the potential production of gum Arabic A. *senygal* in comparison of *A. seyal* has high amounts regarding the regional production**. (Bank of Sudan)**

Commodities	**Unit M.T**	**2010**		**2011**		**2012**		**2013**		**2014**		**(Jan. - June) 2015***	
		الكمية Quantity	**القيمة Value**	**الكمية Quantity**	**القيمة Value**	**الكمية Quantity**	**القيمة Value**	**الكمية Quantity**	**القيمة value**	**الكمية Quantity**	**القيمة Value**	**الكميةQuantity**	**القيمة Value**
Gum Hashab	**M.T**	**12,194**	**16,371**	**42,101**	**77,523**	**13,505**	**43,892**	**28,025**	**92,531**	**21,904**	**62,176**	**26,332**	**35,046**
Gum Talha	**M.T**	**4,214**	**3,833**	**1,817**	**3,057**	**22,738**	**22,738**	**32,316**	**42,242**	**37,829**	**34,800**	**34,268**	**22,514**

Specifications: Gum Hashab and Gum Talha

The definition of Gum Arabic according to the Codex Alimentarius Commission at its 23rd Session in Rome ,1999 was as follows: "Gum Arabic is a dried exudation obtained from the stems and branches of A. senegal (L) or A. seyal (fam. Leguminosae)"

This definition put two gums obtained from two different botanical sources and bear completely different physicochemical properties under one name "gum Arabic". It is intended herein to summarise the differences between these two gums hence substantiate the claim that they cannot be included under one name "gum Arabic"

The quality of gum Arabic(*A. senegal*)must conform to international specifications, which state the specific optical rotation and nitrogen content (-26° to -34° and 0.26% - 0.39%). The quality parameters must be adhered to, by both the producers and the processing enterprises (Anderson et al., 1990, 1991).

Optical rotation isused to determine the nature of sugars in gum arabic obtained from A.senegal variety senegal. The specifications state that the best quality of gum arabic must have negative optical rotation with the range of -26° to -34°. Nitrogen content in gum arabic determines the number of amino acid compositions with the range of 0.26 to 0.39% (FAO, 1990).

Acacia seyal (Gum Talha) has lower Rhamnose and Glucuronic acid contents, higher Arabinose, and 4-O-methyl Glucuronic acid contents than gum from Acacia senegal. Acacia seyal gum contains a lower proportion of nitrogen and the specific rotations are very different+45 to +60. The amino acid compositions are similar with hydroxyproline and serine the major constituents

The regulatory specifications for gum arabic (*Acacia senegal*) are superficial and inadequate to ensure that it is not adulterated with non-permitted gums from other botanical sources. Moreover, the existing specifications do not give the consumer the essential assurance, fundamental to food safety evaluation principles, that the nature and quality of gum arabic used in foodstuffs always conforms to that of the Test Article selected for the toxicological studies which justified the current status ('ADI not specified') of gum arabic as a permitted food additive.

The current specification that gives Acacia senegal and Acacia seyal the same INS 414 will encourage farmers/producers to rely on collecting Acacia seyal, which is wild, and not owned by producers, subjected to natural and man-made fires and not integrated within farming systems. The consequences are: gradual abandonment of the traditional gum arabic, *(Acacia Senega*l), tree stands, loss of the current and potential production of the well-known gum Arabic (Acacia senegal) gum that has an ADI, loss of the local knowledge subjecting the trees to felling for fuel, wood and other domestic needs which will result in poor soil fertility, food insecurity and poverty, and overall loss of the gum arabic industry.

Reference:

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[14] GAC, Gum Arabic Company (1996) Paper Presented on Problems and Constraints of Marketing Gum Arabic. Gum Arabic Conference, Friendship Hall (19 October 1996), Department of Research and Statistics, Gum Arabic Company, Paper No. 9/96, Khartoum, Sudan, 8.

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- Food Addit Contam. 1990 May-Jun;7(3):303-21.
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  Accepted 19 January, 2010

The Sudanese Standards & Metrology Organization (SSMO) is a scientific supervisory organization; its function is to prepare national standards by specialized technical committees in collaboration with related authorities. These standards are prepared by Sudanese gums committee.

A. SPECIFICATION GUM ARABIC (ACACIA SENYGAL) HASHAB GUM

1. SCOPE:

This Sudanese standard applies to the dry exudates from the trees *Acacia sengal var.senegal,* different commercial grades.

2. SYNONYMS:

Kordofan gum and Hashab gum

3. DEFINITIONS:

3.1. Gum Arabic is the dry exudates obtained from the stems and branches of *Acacia senegal var. Senegal* (L) Willdenow (fam. *Leguminosae*). It consists mainly of salts of an acidic arabino- galactan protein complex which on hydrolysis yields galactose, arabinose, rhamnose, glucuronic acid and4-O- methyl glucuronic acid.

3.2. Prebiotic is a non digestible food ingredient that beneficially affects the host by selectively stimulating the growth and /or activity of one or a limited number of beneficial bacteria in the colon, and thus improves host health.

4. DESCRIPTION:

Gum Arabic is a pale white to yellowish –orange solid, which breaks with a glassy fracture. It is odorless and slightly acidic. It may contain extraneous materials such as sand and pieces of bark.

5. COMMERICIAL GRADES:

- Spray Dried Powder Grade, Sudanese standard SDS 139/2011.
- Hand Picked Selected Grade (HPS) Sudanese standard SDS 124/2011.
- Clean Grade, Sudanese standard SDS 123/2011.
- Kibbled Grade, Sudanese standard SDS137/2011.
- Mechanical Powder Grade, Sudanese standard SDS138/2011.
- Dust Grade, Sudanese standard SDS 125/2011.

6. FUNCTIONAL USES:

6.1. Gum Arabic is used as:

6.1.1. A food additive for emulsification, encapsulation, stabilization and thickening.

6.1.2. A food Ingredient, in dietetic foods intended for special medical purposes dietetic foods, e.g., supplementary foods for dietary use, under the conditions of good manufacturing practices (GMP).

6.1.3. Gum Arabic has some other general and technical applications such as inks, textiles sizing and dying, paints, lithography and matches …etc.

7. TECHNICAL REQUIREMENTS:

7.1. IDENTIFICATION TESTS:

7.1.1. It is highly soluble in water, gives up to 50% solution, but insoluble in ethanol.

7.1.2. Should pass hydrolysis products test.

7.13. Specific optical rotation $[a]^{D}{}_{25\,c}$ should be in the range of (-22) to (-34).

7.1.4. Loss in drying should not exceed15 %(105c, 5hrs).

7.2. PURITY TESTS:

Purity test are carried out on dry weight basis.

7.2.1. Total ash should not exceed 4%.

7.2.2. Nitrogen content should be in the range of 0.24to 0.41%.

7.2.3. Protein content should be in the rangeof 1.58 to 2.7% using nitrogen conversion factor (NCF) of 6.6.

7.2.4. Arsenic should not exceed3 mg/kg.

7.2.5. Lead should not exceed10mg/kg.

7.2.6. Heavy metals should not exceed 40mg/kg.

7.2.7. It should not contain starch and dextrin.

7.2.8. It should be free from tannins.

7.3. MICROBIOLGICAL CRITERIA:

7.3.1.It should give a negative result for salmonella sp. per test.

7.3.2. It should give a negative result for E. coli per one gram.

8. PACKING:

8.1**.** Jute bags of 50kg capacity.

8.2. Polypropylene bags lined with foods grade polyethylene of 25-50 kg capacity.

8.3. Multi –layer paper bags lined with food grade 25-50 kg capacity.

8.4. As agreed, upon, between customer and supplier.

9. Labeling:

It should comply with the Sudanese Standard SDS 2889/2007 and indicates:

- Product Name.
- Product Grade.
- Name and address of exporting Company.
- Net weight.
- Season of production.
- Storage Conditions.
- Country of origin.

10. STORAGE:

Should be stored in a properly constructed warehouse, under clean, cool and dry conditions according to the Sudanese Standard SDS 3891/2007.

11. Shelf life:

Unlimited under the appropriate packing and storage conditions mentioned in 8and 10.

12. Sampling Method:

Sampling should be carried out according to Sudanese Standard Sampling method of Gums SDS 145/2011.

13. Testing Methods:

Testing should be carried out according to the following Sudanese standards

13.1 Solubility Tests of Gums SDS 146/2011

13.2 Determination of Sugar in Gums by HPLC SDS 147/2011

13.3 Determination of Loss on drying in Gums SDS 148/2011

13.4. Determination of total ash in Gums SDS 149/2011

13.5. Determination of Specific Optical rotation in gum 152/2011.

13.6. Determination of Nitrogen and estimation of protein in gums SDS 153/2011

13.7. Determination of Heavy metals in gum SDS 154/2011.

13.8. Determination of Glucuronic acid content in gums SDS 155/2011

13.9. Detection of starch and Dextrins in Gum SDS 157/2011.

13.10. Detection of Tannins in Gum, SDS 158/2011.

B. GUM ARABIC, CLEAN GRADE

1. SCOPE:

This Sudanese standard applies to the dry exudates from the trees *Acacia senegal var. senegal,* clean grade.

2. SYNONYMS:

Acacia senegal ,and Hashab and Kordofan gum.

3. DEFINITIONS:

3.1. Gum Arabic is the dry exudates obtained from the stems and branches of *Acacia senegal var. senegal(*L) Willdenow (fam. *Leguminosae*). It consists mainly of salts of an acidic arabino- galactan protein complex which on hydrolysis yields galactose, arabinose, rhamnose, glucuronic acid and 4-O- methyl glucuronic acid.

4. DESCRIPTION: Gum Arabic , clean grade:

Medium to small size nodules and tears and broken pieces of gum arabic.

5. Functional Uses:

Emulsifier, stabilizer, thickening and encapsulating agent and some other general and technical applications.

6. CHARACTERISATION:

6.1. IDENTIFICATION

6.1.1 Solubility: It is highly solublein water gives up to 50% solution and insoluble in ethanol

6.1.2 Hydrolysis products: - Passes test**.**

6.1.3 Specific rotation: $[.]^{D}_{25c}$ (-22) to (-34)

6.2. Purity:

6.2.1 Loss in drying: - Not more than 15% (105c, hrs).

6.2.2 Total Ash - Not more than 4%

*test carried out on dry weight basis

6.2.3. Nitrogen Content - 0.24 to 0.41%

6.2.4. Protein content - 1.58to 2.7%

6.2.5. **Arsenic -** Not more than 3mg/kg

6.2.6 Lead - Not more than 10 mg/kg

6.2.7. Heavy metals - Not more than 40mg/kg

6.2.8. Starch and dextrin - Passes test

6.2.9. Tannin – bearing gums - passes test

6.3. MICROBIOLOGICAL CRITEREA

6.3.1. *Salmonella sp.* - Negative per test

6.3.2. E. Coli - Negative in one gram

7. Packaging:

- Jute bags of 50kg capacity.
- Polypropylene bags Lined with food grade polyethylene, 25-50 Kg capacity.
- Multi-layered paper bags lined with food grade polyethylene, 25-50 kg capacity.
- As agreed upon between customer and supplier.

8. Labelling: Should be clear and indicates the following**:**

Product Name, Product Grade, Name and address of exporting Company.

Net weight, Season of production, Storage Conditions and Country of origin.

9. Storage:

Should be stored under clean, cool and dry conditions, in a properly constructed warehouse.

10. Shelf life: Unlimited under the appropriate storage conditions mentioned in 9.

11. **Sampling:** Sampling should be carried out according toSudanese standard SDS 145**.**

12. Testing: Testing should be carried out according to Sudanese standards 146,147,148, 149, 152,153, 154, 155, 157, 158, and 528.

SPECIFICATION GUM TALHA (ACACIA SEYAL)

Sudanese Standard: Gum Talha, Clean grade

1. Scope:

This Sudanese standard applies to the dry exudates from the trees of *Acacia seyal* var. *seyal,* clean grade.

2. Synonyms:

Acacia seyal gum, clean grade

3. Definitions:

3.1. Gum talha, is the dry exudate obtained from the stems and branches of *Acacia seyal var. seyal (L)* Del (fam. *Leguminosae*). It consists mainly of salts of an acidic arabino- galactan protein complex which on hydrolysis yields galactose, arabinose, rhamnose, glucuronic acid and 4-O-methyl glucuronic acid.

3.2. Prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of beneficial bacteria in the colon, and thus improves health.

4. Description:

Gum talha, Clean grade is the heterogeneous mixture of variables particles sizes.

5. Functional Uses:

5.1. Gum talha, clean grade is used as:

5.1.1. A food additive for emulsification, encapsulation, stabilization and thickening.

5.1.2. A food ingredient, in dietetic foods intended for special medical purposes, dietetic foods formulae for slimming purposes and weight reduction, e.g. supplementary foods for dietary Uses under the conditions of good manufacturing practices (GMP).

5.1.3. A natural prebiotic

5.1.4. A starting material in the spray dried powder manufacture and concentrate

5.2. Gum talha, clean grade has some other general and technical applications such as inks, textiles, sizing and dying, paints, lithography and pyrotechnics .

6. Technical Requirements:

6.1. Identification Test:

6.1.1. It is highly soluble in water, gives up to 50% Solution but in soluble in ethanol.

6.1.2. Should pass hydrolysis products tests.

6.1.3. Specific Optical rotation $[a]^{D}_{25c}$ should be in the range of (+45) to (+60)

6.1.4 Loss in drying should not exceed 15% (105c, 5hrs)

6.2. Purity Test:

Purity tests are carried out on dry weight basis.

6.2.1. Total ash should not exceed 4%.

6.2.2. Nitrogen content should be in the range of 0 .106% to 0.156%.

6.2.3. Protein content should be in the range of 0.7% to 1.0% using nitrogen conversation factor (NCF) of 6.6 .

6.2.4. Arsenic should not exceed 3mg/kg.

6.2.5. Lead should not exceed10mg/kg.

6.2.6. Heavy metals should not exceed 40mg/kg.

6.2.7. It should not contain starch and dextrins.

6.2.8. It may contain traces of tannins.

6.3. Microbial Criteria:

It should give a negative result for Salmonella sp. per test.

6.3.1. It should give a negative result for E. coli per one gram.

7. Packing: It can be packed in:

- Jute bags of 50kg capacity.
- Polypropylene bags Lined with food grade polyethylene, 25-50 Kg capacity.
- Multi-layered paper bags lined with food grade polyethylene, 25-50 kg capacity.
- As agreed upon between customer and supplier.

8. Labeling:

It should comply with the Sudanese Standard SDS 2889/2011 and indicates:

13 Product Name.

14 Product Grade.

15 Name and address of exporting Company.

16 Net weight.

17 Season of production.

18 Storage Conditions.

19 Country of origin.

9. Storage:

Should be stored in a properly constructed warehouse, under clean, cool and dry conditions according to the Sudanese Standard SDS 3891/2007.

10. Shelf life:

Unlimited under the appropriate packing and storage conditions mentioned in 7 and 9.

11. Sampling Method:

Sampling should be carried out according to Sudanese Standard Sampling method of Gums SDS 145/2011.

12. Testing Methods:

Testing should be carried out according to the following Sudanese standards

12.1. Solubility Tests of Gums SDS 1446/2011

12.2. Determination of Sugar in Gums by HPLC SDS 147/2011

12.3. Determination of Loss on drying in Gums SDS 148/2011

12.4. Determinationof total ash in Gums SDS 149/2011

12.5. Determination of Specific Optical rotation in gum 152/2011.

12.6. Determination of Nitrogen and estimation of protein in gums SDS 153/2011

12.7. Determination of Heavy metals in gum SDS 154/2011.

12.8. Determination of Glucuronic acid content in gums SDS 155/2011

12.9. Detection of starch and Dextrins in Gum SDS 157/2011.

12.10. Detection of Tannins in Gum, SDS 158/2011

SWITZERLAND

Name *of Substance(s):*	**Bacteroides xylanisolvens DSM 23964**
Question(s) to* be *answered by JECFA *(kindly provide* a *brief justification of the request in* case *of re-evaluations)*	Assessment of safety using Bacteroides xylanisolvens DSM 23964 for the production of heat-treated fermented milks. Bacteroides xylanisolvens heat-treated fermented milks, and composite milk products based on these products, shall globally be marketed.

1. Proposal for inclusion submitted by: Bioresco Ltd. Basel, Switzerland

2. Name of substance; trade name(s); chemical name(s): Bacteroides xylanisolvens DSM 23964

3. Names and addresses of basic producers: Avitop GmbH, Robert Rössle Str. 10, D-13125 Berlin, Germany

4. Has the manufacturer made a commitment to provide data? Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Albert Bär PhD,

Bioresco Ltd.,

Bundestrasse 29, CH-4054 Basel, Switzerland

Tel: 41-61-273-7700

6. Justification for use: Use of B. xylanisolvens DSM 23964 for the production of heat-treated fermented milk.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Heat-treated fermented milk in line with Codex Standard 243-2003. This Standard includes heat-treated fermented milks (included concentrated forms), and composite milk products based on these products, for direct consumption or further processing in conformity with the definitions of this Standard.

Especially: Fermented milks (plain), heat-treated after fermentation - Number 01.2.1.2; and composite milk products based on these products, for direct consumption or further processing in conformity with the definitions of Codex Standard 243-2003.

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country (ies)? (Please identify the country(ies))

USA: GRAS Notice No. GRN 000457 of 16 December 2013

Based on the information provided by Avitop, as well as other information available to FDA, the agency has no questions at this time regarding Avitop GmbH's conclusion that pastorized fermented milk and *B. xylanisolvens* DSM 23964 are GRAS under the intended conditions of use.

Product has been placed first on the US market in 4th quarter of 2014.

EU:Scientific Opinion on the safety of 'heat-treated milk products fermented with Bacteroides xylanisolvens DSM 23964' as a novel food (EFSA Journal 2015;13(1):3956).

The Panel concludes that the NF 'heat-treated milk products fermented with *B. xylanisolvens* DSM 23964' is safe for the proposed uses and at the proposed use levels.

COMMISSION IMPLEMENTING DECISION (EU) 2015/1291 of 23 July 2015 authorising the placing on the market of heat-treated milk products fermented with *Bacteroides xylanisolvens* (DSM 23964) as a novel food under Regulation (EC) No 258/97 of the European Parliament and of the Council

9. List of data available

Toxicological data

Metabolic and pharrnacokinetic studies - none

(i) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies with ***B. xylanisolvens*** **DSM 23964**

In vitro **test for gene mutations (Ames test), OECD Guidelines 471** ***in vitro*** **chromosome aberration test using, OECD Guideline 473, 90-day oral toxicity study, OECD Guideline 408**

(ii) Epidemiological and/or clinical studies and special considerations

The safety of the ***B. xylanisolvens*** **fermented milk product** was addressed in one threeweek pilot study and a randomised controlled six weeks trial (RCT).

(iii) Other data with ***B. xylanisolvens*** **DSM 23964**

Abscess formation test in mice

Examination of the presence of **antibiotic resistance genes and plasmids**, potential **virulence genes**, **extracellular enzymes** and **pathogenic factors**, determination of the **adhesion of B. xylanisolvens DSM 23964 to Caco-2 cells**

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

B. xylanisolvens **DSM 23964** by sequencing its 16S rRNA genes by DNA-DNA hybridization, as well as by biochemical tests.The *B. xylanisolvens* strain was deposited at the German Resource Centre for Biological Material (DSMZ). Reference number DSM 23964 (DSMZ, 2010).

Heat-treated fermented milk in line with Codex Standard 243-2003. Pasteurised or ultrahigh-temperature-treated (UHT) milk is used for fermentation with *B. xylanisolvens* DSM 23964. After fermentation, the product is heat treated for one hour at 75 °C to ensure the absence of viable *B.xylanisolvens* DSM 23964.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

Comparison of compositional parameters of skimmed milk fermented with ***B. xylanisolvens*** and of commercial milk products fermented with ***Lactobacillus reuteri, L. rhamnosus*** or yoghurt cultures are available.

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

The **heat-treated fermented milk** is intended to be used in liquid and semi-liquid forms in or as fermented low-fat and skimmed milk products, i.e. fermented milks, buttermilks, yoghurts and yoghurt drinks, and as spray-dried powder to be used like yoghurt powders, e.g. in fillings and coatings of cereals, cereal bars, fruits and nuts. The final heat-treated fermented milk products may also be supplemented with other ingredients such as sugars, flavours, fruit preparations and fibre.

Calculations are based on the US National Health and Nutrition Examination Survey (NHANES) food intake data and the associated Food Commodity Intake Database of raw agricultural consumption data. A conservative scenario was considered in which the heattreated fermented milk was assumed to replace all the yoghurts, buttermilks and acidophilus milks.

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance maybe used (EFSA Journal 2015;13(1):3956):

Table 1: Estimated intake of non-fat milk solids and heat-inactivated *B. xylanisolvens* DSM 23964 for the mean and the 90th percentile consumption of yoghurt by age group

Age group, gender	Non-fat milk solids				*B. xylanisolvens* DSM 23964			
	g per day		mg/kg bw per day		Cells per day [(a)]		Cells/kg bw per day	
	Mean	90th	Mean	90th	Mean	90th	Mean	90th
2–5 years	9.5	16.5	570	1084	3.4×10^{11}	5.9×10^{11}	2.0×10^{10}	3.8×10^{10}
6–10 years	9.6	20.5	357	793	3.4×10^{11}	7.3×10^{11}	1.3×10^{10}	2.9×10^{10}
11–19 years, m	12.7	25.0 [(a)]	225	475 [(a)]	4.5×10^{11}	8.9×10^{11}	0.80×10^{10}	1.7×10^{10}
11–19 years, f	11.0	23.1	190	403	3.9×10^{11}	8.1×10^{11}	0.68×10^{10}	1.4×10^{10}
> 20 years, m	12.1	23.1	147	282	4.3×10^{11}	8.2×10^{11}	0.52×10^{10}	1.0×10^{10}
> 20 years, f	11.7	22.5	171	339	4.2×10^{11}	8.1×10^{11}	0.61×10^{10}	1.2×10^{10}
All	11.4	22.5	225	464	4.1×10^{11}	7.9×10^{11}	0.80×10^{10}	1.6×10^{10}

[(a)] Calculated on basis of the assumption that 100 ml heat-treated fermented low-fat or non-fat milk product contains 14 g non-fat milk solids and 0.5×10^{12} CFU of non-viable *B. xylanisolvens* DSM 23964.

10. Date on which data could be submitted to JECFA: Within two weeks upon request.

UNITED STATES OF AMERICA

Addition to the JECFA Priority List

The United States proposes the inclusion of 83 flavors on the JECFA Priority List, which include 8 new flavors, 20 flavors that were included on the JECFA Priority List at previous CCFA meetings, and 55 flavors for which JECFA had requested additional safety information in order to complete its review. The required information for the flavors (as prescribed in Annex 2 of CL 2015/11-FA) is attached as Appendix I to this letter. The full list of 83 flavors is also attached as Appendix II to this letter. The flavors in Appendix II are sorted by Chemical Group, and are identified as to whether they are new submissions, submissions from previous CCFA meetings, or are substances for which JECFA needed additional data to complete its safety review.

Appendix I - Required Information based on Annex 2 of CL 2015/11-FA

List of 83 flavors (comprising 8 new proposals, 20 flavors previously submitted for inclusion on the JECFA Priority List, and 55 flavors for which JECFA required additional information to complete its safety review)

1. Proposal for inclusion submitted by: The United States

2. Name of substance; trade name(s); chemical name(s): List of 83 flavors (See Appendix II for list of chemical names)

3. Names and addresses of basic producers:

International Organization of the Flavor Industry (IOFI). Flavor producers are members of the International Organization of the Flavour Industry (IOFI). All contacts can be made through IOFI.

4. Has the manufacturer made a commitment to provide data? Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

International Organization of the Flavor Industry (IOFI)
Brussels, Belgium
Sean V. Taylor, Ph.D. (Science Director)
1101 17th Street NW, Suite 700
Washington, DC 20036, P: 202-293-5800
staylor@vertosolutions.net

6. Justification for use: Flavouring ingredients in foods for human consumption

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s): Natural occurrence, Food Categories and Use Levels to be submitted.

8. Is the substance currently used in food that is legally traded in more than one country? (Please identify the countries); or, has the substance been approved for use in food in one or more country? (Please identify the country(ies)) -

Yes (United Sates, European Union and Japan)

9. List of data available (please check, if available)

Toxicological data

(i) Metabolic and pharmacokinetic studies: **Yes**

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in

animals and genotoxicity studies: **Yes**

(iii) Epidemiological and/or clinical studies and special considerations: **Yes**

(iv) Other data Yes, where relevant.

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce) Yes

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance Yes, where relevant

Intake assessment data

(i) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used **Yes**

(ii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used. **Yes**

Other information (as necessary/identified)

10. Date on which data could be submitted to JECFA - **December 01, 2016**

Appendix II. List of 83 flavors for inclusion on JECFA Priority List

CCFA listing History	FEMA No	JECFA No	CAS	Principle Name	Group No	TRS No
	MISCELLANEOUS NITROGEN-CONTAINING SUBSTANCES				J56	TRS 934 TRS 952 TRS 974
New Submission	4793		1446687-20-2	(3*R*,3*S*)-3-[[(4-amino-2,2-dioxido-1*H*-2,1,3-benzothiadiazin-5-yl)oxy]methyl]-*N*-cyclopentyl-2-oxo-3-piperidinecarboxamide		
New Submission	4798		902136-79-2	2-(((3-(2,3-Dimethoxyphenyl)-1*H*-1,2,4-triazol-5-yl)thio)methyl)pyridine		
New Submission	4802		1469426-64-9	(*S*)-1-(3-(((4-amino-2,2-dioxido-1*H*-benzo[c][1,2,6]thiadiazin-5-yl)oxy)methyl)piperidin-1-yl)-3-methylbutan-1-one		
New Submission	4809		1374760-95-8	2-(4-Methylphenoxy)-*N*-(1*H*-pyrazol-3-yl)-*N*-(thiophen-2-ylmethyl)acetamide		
	ALLYL ESTERS				J03	TRS 868
Submitted at 43rd CCFA	4074		6321-45-5	Allyl valerate		
Submitted at 43rd CCFA	4072		20474-93-5	Allyl crotonate		
	SATURATED ALIPHATIC ACYCLIC LINEAR PRIMARY ALCOHOLS, ALDEHYDES, AND ACIDS				J04	TRS 884
Submitted at 43rd CCFA	4432		591-11-7	(+/-) Acetaldehyde ethyl isopropyl acetal		
Submitted at 43rd CCFA	4335			Tridecanal		
Submitted at 43rd CCFA	4528		57743-63-2	Acetaldehyde ethyl isobutyl acetal		
Submitted at 43rd CCFA	4336		5617-64-1	Tridecanoic acid		
Submitted at 43rd CCFA CCFA	4527		851670-40-1	Acetaldehyde di-isobutylacetal		
Submitted at 45th CCFA	4688		851669-60-8	1-Dipropoxyethane		
Submitted at 43rd CCFA CCFA	4334		125187-30-6	Pentadecanoic acid		
Submitted at 43rd	4010			Paraldehyde		

CCFA listing History	FEMA No	JECFA No	CAS	Principle Name	Group No	TRS No
	SATURATED ALIPHATIC ACYCLIC BRANCHED-CHAIN PRIMARY ALCOHOLS, ALDEHYDES, AND ACIDS				J05	TRS 884
New Submission	4795		127793-88-8	(±)-8-Methyldecanal		
New Submission	4803		3085-26-5	8-Methylnonanal		
	LINEAR AND BRANCHED-CHAIN ALIPHATIC, UNSATURATED, UNCONJUGATED ALCOHOLS, ALDEHYDES, ACIDS, AND RELATED ESTERS				J14	TRS 891
New Submission	4787		63196-63-4	*trans*-6-Octenal		
New Submission	4789		4234-93-9	2,6-Dimethyl-5-heptenol		
	CARVONE AND STRUCTURALLY RELATED SUBSTANCES				J16	TRS 891
Submitted at 43rd CCFA	4525		929116-08-5	Pinocarvyl isobutyrate		
Submitted at 43rd CCFA	4515		929222-96-8	Carvyl palmitate		
Submitted at 43rd CCFA	4523		51200-86-3	6-Hydroxycarvone		
	MENTHOL AND STRUCTURALLY RELATED SUBSTANCES				J11	TRS 891 TRS 952
Submitted at 43rd CCFA	4509		2230-90-2	Menthyl formate		
Submitted at 43rd CCFA	4510		86014-82-6	Menthyl propionate		
Submitted at 43rd CCFA	4524		68366-64-3	l-Menthyl butyrate		
Submitted at 45th CCFA	4729		3623-52-7	dl-Isomenthol		
Submitted at 43rd CCFA	4604		406179-71-3	Dimenthyl glutarate		
Submitted at 45th CCFA	4718		28804-53-7	(±)-2-[(2-p-Menthoxy)ethoxy]ethanol		
	MALTOL AND RELATED SUBSTANCES				J52	TRS 934
Submitted at 43rd CCFA	4534		852997-28-5	Ethyl maltol isobutyrate		
	EPOXIDES (RE-EVALUATION)				J57	TRS 934 TRS 974
Old	4657	2147	42134-50-9	2,3-Epoxyoctanal		

CCFA listing History	FEMA No	JECFA No	CAS	Principle Name	Group No	TRS No
Old	4658	2148	58936-30-4	2,3-Epoxyheptanal		
Old	4659	2149	102369-06-2	2,3-Epoxydecanal		
	FURFURYL ALCOHOL AND RELATED SUBSTANCES (RE-EVALUATION)				J23	TRS 901 TRS 974
Old	4544	2099	3857-25-8	5-Methylfurfuryl alcohol		
Old	4537	2100	4359-54-0	Furfural propyleneglycol acetal		
Old	4542	2101	13493-97-5	Furfuryl formate		
Old	4539	2102	39252-05-6	Furfuryl decanoate		
Old		0759	623-21-2	Furfuryl butyrate		
	PYRIDINE, PYRROLE AND QUINOLINE DERIVATIVES (RE-EVALUTION)				J44	TRS 928 TRS 974
Old	4317	2150	2167-14-8	*N*-Ethyl-2-formylpyrrole		
Old	4389	2151	108-47-4	2,4-Dimethylpyridine		
Old	4332	2152	1192-58-1	1-Methylpyrrole-2-carboxaldehyde		
Old	4639	2156	1628-89-3	2-Methoxypyridine		
Old	4721	2158	1186004-10-3	1-(2-Hydroxyphenyl)-3-(pyridin-4-yl) propan-1-one		
Old	4722	2159	1190230-47-7	1-(2-Hydroxy-4-methoxyphenyl)-3-(pyridine-2-yl) propan-1-one		
Old	4723	2160	1190229-37-8	1-(2-Hydroxy-4-methoxyphenyl)-3-(pyridine-2-yl) propan-1-one		
	ALICYCLIC PRIMARY ALCOHOLS, ALDEHYDES, ACIDS AND RELATED ESTERS (RE-EVALUATION)				J32	TRS 913 TRS 960
Old	3557	973	2111-75-3	*p*-Mentha-1,8-dien-7-al		
	FURAN SUBSTITUTED ALIPHATIC HYDROCARBONS, ALCOHOLS, ALDEHYDES, KETONES, CARBOXYLIC ACIDS AND RELATED ESTERS, SULFIDES, DISULFIDES AND ETHERS.(RE-EVALUATION)				J53	TRS 934 TRS 952 TRS 974
Old	3317	1491	3777-69-3	2-Pentylfuran		
Old	3401	1492	3777-71-7	2-Heptylfuran		
Old	4090	1493	83469-85-6	2-Decylfuran		
Old	4174	1494	15186-51-3	3-Methyl-2-(3-methylbut-2-enyl)-furan		
Old	2494	1497	623-30-3	3-(2-Furyl)acrolein		
Old	4175	1499	5555-90-8	3-(5-Methyl-2-furyl)prop-2-enal		

CCFA listing History	FEMA No	JECFA No	CAS	Principle Name	Group No	TRS No
Old	3163	1503	1192-62-7	2-Furyl methyl ketone		
Old	3609	1504	1193-79-9	2-Acetyl-5-methylfuran		
Old	4071	1505	22940-86-9	2-Acetyl-3,5-dimethylfuran		
Old	4083	1507	4208-57-5	2-Butyrylfuran		
Old	2496	1508	6975-60-6	(2-Furyl)-2-propanone		
Old	4192	1509	3194-17-0	2-Pentanoylfuran		
Old	4120	1510	699-17-2	1-(2-Furyl)butan-3-one		
Old	2495	1511	623-15-4	4-(2-Furyl)-3-buten-2-one		
Old	2435	1513	10031-90-0	Ethyl 3-(2-furyl)propanoate		
Old	2198	1514	105-01-1	Isobutyl 3-(2-furan)propionate		
Old	2071	1515	7779-67-1	Isoamyl 3-(2-furan)propionate		
Old	2070	1516	7779-66-0	Isoamyl 4-(2-furan)butyrate		
Old	2865	1517	7149-32-8	Phenethyl 2-furoate		
Old	3159	1520	13679-46-4	Furfuryl methyl ether		
Old	4114	1521	6270-56-0	Ethyl furfuryl ether		
Old	3337	1522	4437-22-3	Difurfuryl ether		
Old	4034	1523	55764-22-2	2,5-Dimethyl-3-furanthiol acetate		
Old	4119	1524	109537-55-5	Furfuryl 2-methyl-3-furyl disulfide		
Old	4056	1525	61295-44-1	3-[(2-Methyl-3-furyl)thio]-2-butanone		
Old	4043	1526	376595-42-5	*O*-Ethyl S-(2-furylmethyl)thiocarbonate		
Old	3535	1495	3782-00-1	2,3-Dimethylbenzofuran		
Old	4095	1496	64280-32-6	2,4-Difurfurylfuran		
Old	2704	1498	874-66-8	2-Methyl-3(2-furyl)acrolein		
Old	3307	1500	31704-80-0	3-(5-Methyl-2-furyl)-butanal		
Old	2492	1501	770-27-4	2-Furfurylidene-butyraldehyde		
Old	3586	1502	65545-81-5	2-Phenyl-3-(2-furyl)prop-2-enal		
Old	3391	1506	10599-70-9	3-Acetyl-2,5-dimethylfuran		
Old	3418	1512	14360-50-0	Pentyl 2-furyl ketone		
Old	2945	1518	623-22-3	Propyl 2-furanacrylate		

CCFA listing History	FEMA No	JECFA No	CAS	Principle Name	Group No	TRS No
Old	3970	1519	114099-96-6	2,5-Dimethyl-3-oxo-(2H)-fur-4-yl butyrate		
Old	4541	2103	53282-12-5	(*E*)-Ethyl 3-(2-furyl)acrylate		
Old	4540	2104	1197-40-6	di-2-Furylmethane		
Old	4543	2105	4265-25-2	2-Methylbenzofuran		

CONSEIL EUROPEEN DE L'INDUSTRIE CHIMIQUE (CEFIC)

Name of Substance(s):	**Ferric orthophosphate ($FePO_4 \times H_2O$)**
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Establishment of specifications. Countries are starting to create their own quality criteria. Codex standards should refer to a JECFA specification with regard to trade burdens. Different ways of production need to be reflected by the specification.

1. Proposal for inclusion submitted by:

CEFIC - Phosphoric Acid and Phosphates Association (PAPA)
Av. E. Van Nieuwenhuyse 4 / box 1
B - 1160 Brussels

2. Name of substance; trade name(s); chemical name(s):

CAS#10045-86-0; iron(iii)orthophosphate

CAS numbers for the hydrate form should be included in the monograph:

- CAS 13463-10-0 (2-hydrate; synthetic form)
- CAS 14567-75-0 (2-hydrate; natural form)

3. Names and addresses of basic producers:

Phosphoric Acid and Phosphates Association (PAPA), representing the basic producers
Marc Vermeulen
Av. E. van Nieuwenhuyse, 4, 1160 Brussels
Tel. 32-26767446
Fax. 32-26767359
e-mail:mve@cefic.be / www.cefic.org

4. Has the manufacturer made a commitment to provide data? - Yes

5. Identification of the manufacturer that will be providing data:

Phosphoric Acid and Phosphates Association (PAPA), representing the basic producers
Marc Vermeulen
Av. E. van Nieuwenhuyse, 4, 1160 Brussels
Tel. 32-26767446
Fax. 32-26767359
e-mail: mve@cefic.be / www.cefic.org

6. Justification for use

Recommended use as a nutrient source of iron according to CAC/GL 10-1979

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s)

In line with the recommendations on iron from Codex Standards on

- Processed Cereal Based Food for Infants and Young Children and in foods which could be fortified with iron in line with nutritional requirements up to 14mg Fe/p/d.

The use comprises FC 13.2 and 13.6

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the countries)

Not applicable

9. List of data available

Toxicological data - Data available

Technological data

i. Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

FCC specification

ii. Technological and nutritional considerations relating to the manufacture and use of the listed substance

It is used as a nutrient (source of iron) which could be used in line with the recommendations for daily iron intakes

Intake assessment data - Not applicable – data for iron in general is relevant;

Other information as necessary

Data on bioavailability (in vivo) is available in the public domain

10. Date on which data could be submitted to JECFA - Immediately on request

Name of Substance(s)	**Ferric pyrophosphate ($Fe_4(P_2O_7)_3 \times H_2O$)**
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Establishment of specifications (and maybe assessment as nutrient source – as applicable) for the use as nutrient (source of iron) Some countries (e.g. China, Japan) have created their own quality criteria aside from FCC. Codex document CAC/GL 10-1979 currently refers to FCC quality for the substance and we would like to see criteria harmonized within a JECFA specification in order to avoid technical trade burdens. Different ways of production need to be reflected by the same specification which is currently not in line with Chinese or Japanese specifications for that nutrient.

1. Proposal for inclusion submitted by:

CEFIC - Phosphoric Acid and Phosphates Association (PAPA)
Av. E. Van Nieuwenhuyse 4 / box 1
B - 1160 Brussels

2. Name of substance; trade name(s); chemical name(s):

CAS#10058-44-3; tetra-iron tris (pyrophosphate)

3. Names and addresses of basic producers:

Phosphoric Acid and Phosphates Association (PAPA), representing the basic producers
Marc Vermeulen
Av. E. van Nieuwenhuyse, 4, 1160 Brussels
Tel. 32-26767446
Fax. 32-26767359
E-mail: mve@cefic.be /www.cefic.org

4. Has the manufacturer made a commitment to provide data? - Yes

5. Identification of the manufacturer that will be providing data:

Phosphoric Acid and Phosphates Association (PAPA), representing the basic producers
Marc Vermeulen
Av. E. van Nieuwenhuyse, 4, 1160 Brussels
Tel. 32-26767446
Fax. 32-26767359
E-mail: mve@cefic.be / www.cefic.org

6. Justification for use:

Use as a nutrient source for iron according to CAC/GL 10-1979

7. Food products and food categories within the GSFA in which the compound is used as a food additive or as an ingredient, including use level(s):
In line with the recommendations on iron from Codex Standards on

- Infant Formula and Formulas for Special Medical Purposes Intended for Infants
- Follow-up Formula
- Processed Cereal Based Food for Infants and Young Children
- Canned Baby Food
- Food for Special Medical Purposes other than Infant Formula and in foods which could be fortified with iron in line with nutritional requirements up to 14mg Fe/p/d.

The use mainly comprises FC 13.1-13.6

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the countries)

Yes: EU, USA, JAPAN, CHINA

9. List of data available

Toxicological data

Read-across from other iron salts with comparable relative bioavailability; data available

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

Similar to FCC specification, but with different assay (22.0-26.0% Fe) and different loss on ignition (<29.0% @800°C for 30min) in order to reflect different ways of production.

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance

It is used as a nutrient (source of iron) which could be used in line with the recommendations for daily iron intakes.

Intake assessment data - Not applicable – data for iron in general is relevant;

Other information as necessary

Data on bioavailability (in vivo) is available in the public domain

10. Date on which data could be submitted to JECFA - Immediately on request

ENZYME TECHNICAL ASSOCIATION (ETA)

The Enzyme Technical Association (ETA), a non-governmental organization recognized by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), respectfully submits the attached request for the addition of D-allulose-3-epimerase to the list of substances to be evaluated by JECFA.

D-allulose 3-epimerase, an enzyme manufactured by Matsutani Chemical Industries, is a processing aid for the production of D-allulose or ketose sugars. The enzyme epimerizes D-fructose on C3 position to D-allulose. The enzyme is widely found in nature.

As indicated in the attached form, toxicologic and technical data are available for the Committee to review. Should you have any questions regarding this submission, please do not hesitate to contact my colleague Gary L. Yingling at gyingling@morganlewis.com, or by phone at (202) 739-5610.

Name of Substance(s):	D-allulose 3-epimerase
Question(s) to be answered by JECFA (provide a brief justification of the request in case of re-evaluations)	Safety assessment and establishment of specifications

1. Proposal for inclusion submitted by: Enzyme Technical Association

2. Name of substance; trade name(s); chemical name(s):

- Systematic Name: D-psicose 3-epimerase.
- Common Name: D-allulose 3-epimerase.
- Trade Name: Matsurase FE

3. Names and addresses of basic producers:

Matsutani Chemical Industry Co. Ltd.
5-3 Kitaitami, Itami-city, Hyogo,
Japan 664-8508

4. Has the manufacturer made a commitment to provide data? Yes

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Yuma Tani
Deputy Manager, Overseas R&D
Matsutani Chemical Industry Co. Ltd.
5-3 Kitaitami
Itami-city, Hyogo, Japan 664-8508

6. Justification for use:

D-allulose 3-epimerase is a processing aid for the production of D-allulose or ketose sugars. The enzyme epimerizes D-fructose on C3 position to D-allulose. The enzyme is widely found in nature.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

D-allulose 3-epimerase can be used for epimerization of fructose to produce allulose. The average dosage of the enzyme depends on the process conditions and on the desired properties of the final product. A typical use level would be 10,000 – 30,000 FEU per kg allulose dry matter, or 20-60 g of the enzyme preparation in liquid form per kg allulose dry matter.

Allulose (US FDA GRAS Notice 498) is intended to be used in a wide range of food applications include cereals, chewing gum, confections & frostings, dressings for salads, jams & jellies, sugar, sugar substitutes (carrier), and various low- calorie or dietetic foods including low-calorie, reduced-calorie, sugar-free beverages(non-alcoholic), cereals, frozen dairy desserts (ice cream, soft serve, sorbet), yogurt and frozen yogurt, gelatins, pudding & fillings, hard candies, soft candies, and sweet sauces & syrups.

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies))

D-allulose 3-epimerase can be used for epimerization of fructose to produce allulose. Allulose has been reviewed by the U.S. Food and Drug Administration in two separate GRAS Notifications, GRN 400 and GRN 498. Both applications received letters of no objection from the FDA. A GRAS notification for the enzyme in question, D-allulose 3-epimerase, has been submitted for review to the FDA.

9. List of data available (please check, if available)

Toxicological data

i. Metabolic and pharmacokinetic studies

- Digestibility search was conducted

ii. Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

Available studies:

- 90 day oral toxicity study
- Bacterial reverse mutation (Ames) assay
- *In vitro* micronucleus test in cultured human lymphocytes

iii. Epidemiological and/or clinical studies and special considerations

- Not available

iv. Other data

- Not available

Technological data

i. Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

- Available

ii. Technological and nutritional considerations relating to the manufacture and use of the listed substance.

- The enzyme is not intended for digestion. A digestibility search indicates that should the enzyme be consumed, its proteins would be digested by human enzymes and therefore would have no impact on nutritional parameters.

Intake assessment data

i. Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

- Available

ii. Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

- Available

Other information (as necessary/identified)

10. Date on which data could be submitted to JECFA: - Information will be available by December 1, 2016.

INTERNATIONAL ASSOCIATION OF COLOR MANUFACTURERS (IACM)

Name of Substance(s):	***Spirulina Extract***
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	***Safety assessment and establishment of specifications for use as color.***

1. Proposal for inclusion submitted by: International Association of Color Manufacturers

2. Name of substance; trade name(s); chemical name(s): Spirulina Extract

3. Names and addresses of basic producers:

Hainan DIC Microalgae Co., Ltd.(Office)
Room 601-603, Baohua Harbour View Hotel, 69 Binhai Ave., Haikou, Hainan Province, 570105,
People's Republic of China
Telephone No.: +86-898-66769458
(Factory)
Xinmin, Jiazi-Town, Qiongshan district, Haikou, Hainan Province, 571145,
People's Republic of China
Telephone No.: +86-898-63800808

Earthrise Nutritionals LLC (Office)
2151 Michelson Dr., Suite 258, Irvine, CA 92612, USA
Telephone No.: +1-949-6230920(Factory)
113 E. Hoober Rd., Calipatria, CA 92233, USA
Telephone No.: +1-760-3485027

4. Has the manufacturer made a commitment to provide data? IACM or its member companies can provide the available published data in a submission dossier.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

IACM contact is Sarah Codrea, Executive Director, IACM, 1101 17th St NW, Suite 700 Washington DC 20036, 202-293-5800, Email: scodrea@vertosolutions.net.

6. Justification for use: Used as a food color.

7. Food products and food categories within the GSFA in which the substance is used as a food additive or as an ingredient, including use level(s):

Spirulina Extract is not currently listed in the GSFA, however in the US, Spirulina extract may be safely used for coloring confections (including candy and chewing gum), frostings, ice cream and frozen desserts, dessert coatings and toppings, beverage mixes and powders, yogurts, custards, puddings, cottage cheese, gelatin, breadcrumbs, and ready-to-eat cereals (excluding extruded cereals), at levels consistent with good manufacturing practice. We expect these categories to be analogous to the following GSFA food categories: Unripened cheese (01.6.1); Dairy-based desserts (e.g., pudding, fruit or flavored yogurt (01.7); Fruit-based desserts, including fruit-flavored water-based desserts (04.1.2.9); Confectionary (05.0); Breakfast cereals, including rolled oats (06.3); Cereal and starch based desserts (e.g., rice pudding, tapioca pudding) (06.5); Bread-type products, including bread stuffing and bread crumbs (07.1.4); Egg-based desserts (e.g., custard) (10.4); and Concentrates (liquid or solid) for water-based flavored drinks (14.1.4.3). Use levels are provided below in the listing of available intake assessment data.

8. Is the substance currently used in food that is legally traded in more than one country? (please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies))

Spirulina Extract is currently approved for use as a food color in the US at 21 CFR 73.530, as well as in China, Japan, and Korea.

9. List of data available (please check, if available)

IACM is prepared to provide all toxicological, exposure and specification data that is available, including that of which is outlined below.

Toxicological data

i. Metabolic and pharmacokinetic studies

ii. Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies

Short-term Studies

G.A. Chamorro, et al. (1988) Short-term toxicité study of Spirulina in F3b generation rats. J. Toxicol. Clin. Exp., Vol. 8(3), pages 163-167.

Sub-chronic Studies

Akhilender Naidu, K. et al. (1999) Toxicity Assessment of Phycocyanin - A Blue Colorant from Blue Green Alga Spirulina platensis. Food Biotechnol. Vol. 13(1), pages 51-66.

Chamorro, G.A. et al. (1988) Subchronic Toxicity Study in Rats Fed Spirulina. J. Pharm. Belg. Vol. 43(1), pages 29-36.

Hutadilok-Towatana, N. et al. (2008) A subchronic toxicity study of Spirulina platensis, Food Sci. Technol. Res., Vol. 14 (4), pages 351 – 358.

Hutadilok-Towantana, N. et al. (2010) Evaluation of the toxicity of Arthrospira (Spirulina) platensis extract. J. Appl. Phycol. Vol. 22, pages 599-605.

Salazar, M. et al. (1998) Subchronic toxicity study in mice fed Spirulina maxima, J. Ethnopharmacol., Vol. 62(3), pages 235-241.

Chronic Studies

Boudene, C. Collas, E. and Jenkins C. (1976) Recherche et dosage de divers toxiques minereaux dans les algues spirulines de differentes origins, et evaluation de la toxicite a long terme chez le rat d'un lot algues spirulines de provenance Mexicaine. Ann. Nutr. Alim. 30, pages 577-588.

Chamorro G.A., et al. (1988) Etude de la toxicite' chronique de la Spiruline chezle rat. Med. Nutr., Vol. 24, pages 104-106.

Yang, Y. et al. (2011) In vitro and in vivo safety assessment of edible blue-green algae. Nostoc commune var. spheroides Kützing and Spirulina platensis, Food and Chem. Toxicol. Vol. 49(7), pages 1560-1564.

Yoshino, Y. et al. (1980) The Chronic Intoxication Test on Spirulina Product Fed to Wistar-Strain Rats, Jap. J. Nutr., Vol. 38(4), pages 221-225.

Reproductive and Developmental Studies

Chamorro, G.A. et al. (1987) Evaluation teratologique de la Spirulina chez le hamster, Belg. J. Food Chem. Biotech., Vol. 42, pages 188-191.

Chamorro, G.A. et al. (1988) Short-term toxicity study of Spirulina in F3b generation rats. J. Toxicol. Clin. Exp., Vol. 8(3), pages 163-167.

Chamorro, G.A. et al. (1989) Estudio Teratogenico de Spirulina en Rata. Arch Latinoam Nutr. Vol. 39(4), pages 641-649.

Chamorro G.A. and Salazar M. (1990) Estudio Teratogenico de Spirulina en Raton. Arch. Latinoam., Vol. 40(1), pages 86-94.

Chamorro, G.A. et al. (1997) Reproductive and Peri- and Postnatal Evaluation of Spirulina maxima in Mice, J. Appl. Phycol., Vol. 9(2), pages 107-112.

Salazar, M. et al. (1996) Effect of Spirulina maxima Consumption on Reproduction and Peri and Postnatal Development in Rats, Food Chem. Toxicol., Vol. 34(4), pages 353-359.

Genetic Toxicity Studies

Chamorro, G.A. and Salazar, M. (1996) Dominant Lethal Study of Spirulina maxima in Male and Female Rats after Short-term Feeding. Phytotherapy Res., Vol.10, pages 28-32

G.A. Chamorro and M. Salazar (1989) Dominant Lethal Assay of Spirulina maxima in Male CD-1 Mice after Short-Term and Prolonged-Term Feeding, J. Food Protect., Vol.52(2), pages 125-127.

M. Salazar and G.A. Chamorro (1990) Study of Lethal Dominant of Spirulina maxima in Male Rats, Sciences Des Aliments, Vol.10, pages 713-718.

iii. Epidemiological and/or clinical studies and special considerations

Nutrition Related Studies (Human)

Borowitzka, MA, (2009) Spirulina in Human Nutrition and Health. M.E. Gershwin, A. Belay (eds). Vol. 21, pages 747-748.

Gershwin, M.E. and Belay, A. Editors. (2008) Spirulina in Human Nutrition and Health. CRC Press, Boca Raton, FL. A review of this book was published in the Journal of Applied Phycology.

Mani, UV, et al. (2008) Chapter 4: Therapeutic Utility of Spirulina, in Therapeutic Utility of Spirulina. ME Gershwin and A Belay (eds), pages 72-77.

Nakaya, N.Y. et al. (1988) Cholesterol lowering effect of Spirulina. Nutr. Rep. Int., Vol. 37, pages 1329-1337.

Simpore, J. et al. (2006) Nutrition rehabilitation of undernourished children utilizing Spirulina and Misola, Nutrition Journal, Vol. 5, pages 1-7.

iv. Other data

Animal Nutrition Studies

Fevrier C. and Seve B. (1976) Essais d'incorporation de spiruline (Spirulina maxima) dans les aliments des porcins. Ann. Nutr. Aim. Vol. 29, pages 625-650

Rashmi Kapoor and Usha Mehta, (1993) Effect of Supplementation of Blue Green Alga (Spirulina) on Outcome of Pregnancy in Rats. Plant Foods Human Nutr. Vol. 43, pages 29-35.

Reviews
Orio Ciferri (1983) Spirulina, the Edible Microorganism. Microbiological Reviews, Vol. 47, No. 4, p. 551-578. American Society for Microbiology.

Technological data

(iii) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)

According to US regulations, spirulina extract must conform to the following specifications and must be free from impurities, other than those named, to the extent that such other impurities may be avoided by good manufacturing practice:

- **Lead, not more than 2 milligrams per kilogram (mg/kg) (2 part per million (ppm));**
- **Arsenic, not more than 2 mg/kg (2 ppm);**
- **Mercury, not more than 1 mg/kg (1 ppm); and**
- **Negative for microcystin toxin.**

(iv) Technological and nutritional considerations relating to the manufacture and use of the listed substance

Intake assessment data

(v) Levels of the listed substance used in food or expected to be used in food based on technological function and the range of foods in which they are used

A sample of use levels is included here; complete information will be provided in a full monograph.

Food Description	**Typical Use Level, Spirulina Concentrate**
Confection Sugar	≤ 2.0%
Syrup, honey, jams, jellies, fruit butter, molasses	≤ 2.0%
Marshmallows	1 - 10%
Sugar and sugar substitute	≤ 2.0%
Chewing gum	≤ 5.0%
Ice cream, ice milk, frozen yogurt, sherbets	0.3 - 1%
Frozen ice/pops	0.3 - 1%
Cake frosting/icing	3 - 4%
Baking decorations	1 - 2.5%
Batter mixes, breadcrumbs	≤ 3.0%
Other dessert toppings	≤ 2.0%
Pie, custard, cream, fillings	≤ 2.0%
Drink mixers (without alcohol)	0.5 - 2%
Yogurt, cottage cheese, custard, gelatin, pudding	1 - 2%
Extruded cereals	1 - 10%
Coated cereals	3 - 5%
Baking candies	≤ 4.0%
Hard and soft candies	0.5 - 1.5%
Hard-panned chocolates	1 - 2.5%
Fruit gum	0.5 - 1.5%

(vi) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used.

Data collected from 2003 to 2008 by the US National Health and Nutrition Examination Survey (NHANES) will be provided.

Other information (as necessary/identified)

10. Date on which data could be submitted to JECFA. IACM or its member companies can provide this data by December 2016.

INTERNATIONAL SPECIAL DIETARY FOODS INDUSTRIES (ISDI)

INFORMATION ON GELLAN GUM (INS 418) REQUESTED FOR JECFA EVALUATION FOR USE IN INFANT FORMULA AND FORMULAE FOR SPECIAL MEDICAL PURPOSES INTENDED FOR INFANTS

1. Proposal for inclusion submitted by: International Special Dietary Foods Industries (ISDI)

2. Name of compound; trade name(s); chemical name(s):

Gellan Gum; trade name is Keltrol ®,Kelcogel®; IUPAC Name is Gellan Gum , INS No. 418; CAS#: 71010-52-1; E275-117-5

3. Names and addresses of basic producers (of the infant formula):

Abbott Nutrition, 625 Cleveland Avenue Columbus OH 43215, USA

4. Has the manufacturer made a commitment to provide data? Yes.

5. Identification of the manufacturer that will be providing data (Please indicate contact person):

Brinda Mahadevan, Ph.D Manager, Regulatory Affairs Abbott Nutrition
3300 Stelzer Road
Columbus OH 43219, USA Phone: 614-624-3089
Fax: 614-727-6245
E-mail: brinda.mahadevan@abbott.com

6. Justification for use:

Gellan gum acts as a stabilizer in ready-to-feed infant formula, or concentrated liquid products to improve physical stability through mechanisms such as maintaining homogeneity or minimizing ingredient sedimentation. Gellan gum helps to keep minerals such as calcium and phosphorus in suspension and prevents physical separation of the product.

7. Food products and food categories within the GSFA in which the compound is used, including use level(s):

Proposed for use as a stabilizer up to 100 mg/kg, as consumed, in food category 13.1 infant formulae, follow-on formulae and formulae for special medical purposes for infants

8. Is the compound currently used in food that is legally traded in more than one country? (please identify the countries); or, has the compound been approved for use in 2 or more countries (please identify the countries)?

Gellan gum is an approved food additive in the US. It's an approved additive for specific categories in Canada and is recognized by EU and Codex in other categories. Gellan gum is currently used in infant formula in the US.

9. List of data available (please check, if available):

Toxicological data

(i) Metabolic and pharmacokinetic studies

(ii) Short-term toxicity

(iii) Epidemiological and/or clinical studies and special considerations

(iv) Other data

Technological data

(i) Specifications for the identity and purity of the listed compounds (specifications applied during development and toxicological studies; proposed specifications for commerce)

(ii) Technological and nutritional considerations relating to the manufacture and use of the listed compound

Intake assessment data
(i) Levels of the listed compound used in food or expected to be used in food based on technological function and the range of foods in which they are used

(ii) Estimation of dietary intakes based on food consumption data for foods in which the compound may be used

Other information as necessary

10. Date on which data could be submitted to JECFA: December 1, 2016