CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 7 **CX/FA 18/50/12**

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD ADDITIVES

Fiftieth Session

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

Replies to CL 2017/48-FA of China, European Union, Japan, Sudan, EU Specialty Food Ingredients, IACM, ICBA, IOFI and ISC

CHINA

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	Gellan gum (INS 418)
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Request: JECFA is asked to consider removing the limit for ethanol from the specification of "Gellan gum" (INS 418). Justification: In 2013, the European Union proposed an amendment to the gellan gum specification to recognise ethanol as an alternative solvent in the production of gellan gum (CX/FA 13/45/16). This request did not include a proposal for a numerical limit for ethanol. As a result of this request, JECFA, at its 79th session (TRS 990-JECFA79/56), considered that use and revised the INS 418 specification to include the use of ethanol as an alternative to 2-propanol, but additionally set a numerical maximum limit of 50 mg/kg for this solvent which, in relation to safety in the food additive context, is regularly considered a GMP solvent (14th JECFA; FAO Nutrition Meeting Report Series 48a, WHO/FAO/Food Add/70.39). China additionally notes that neither the Chinese legal specification for gellan gum (GB 25535), nor the USA FCC (10th edition), nor the current E 418 purity criteria of the EU set a numerical limit for residual ethanol in gellan gum. With this reply to CL 2017/48-FA, China respectfully requests that JECFA considers amend the provision for ethanol in the INS 418 specification as a numerical limit may not be needed.

1. Proposal for inclusion submitted by:

PR China, China National Center for Food Risk Assessment, Beijing, China.

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

Gellan Gum, INS 418

3. Names and addresses of basic producers:

Zhejiang DSM Zhongken Biotechnology Co Ltd, 314515, Gaoqiao economic zone, Tongxiang city, Zhejiang

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):

Zhejiang DSM Zhongken Biotechnology Co Ltd, 314515, Gaoqiao economic zone, Tongxiang city, Zhejiang province, Mr Wen Fang wen.fang@dsmzk.com

6. Justification for use:

Gellan gum is a food additive with function thickener, gelling agent, stabiliser as mentioned in its currently endorsed INS 418 monograph. There is no change in uses to previous evaluations by JECFA (37th, 49th, 79th session).

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):

Gellan gum INS 418 is listed in table 3 of the GSFA as it is a food additive with an ADI "not specified". Its use level is "GMP".

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. Gellan gum is permitted and used in the PR China, and to the best of our knowledge also permitted for use in foods in the USA, European Union, Japan, Malaysia, Argentina, Brasil, Chile, Mexico, Morokko, the Middle Eastern Gulf counties of the GCC, and others.

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

Toxicological data

Not applicable as the request concerns only a change in an existing parameter in the gellan gum specification INS 418. However, reference is made to the toxicological monograph that had been prepared by JECFA and which is publicly available on WHO/JECFA website. The reference to the report is FAS 28-JECFA 37/289.

(i) Metabolic and pharmacokinetic studies Not applicable for the present request; however general reference is made to FAS 28-JECFA 37/289 for such information.

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies Not applicable for the present request; however general reference is made to FAS 28-JECFA 37/289m for such information

(iii) Epidemiological and/or clinical studies and special considerations Not applicable for the present request; however general reference is made to FAS 28-JECFA 37/289

(iv) Other data Not applicable; see FAS 28-JECFA 37/289.

Technological data

(v) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce). Technical and regulatory information addressing the use of ethanol as a processing aid in the manufacture of gellan gum with a focus to justify a deletion of a numerical ethanol limit, or to raise this limit to GMP.

(vi) Technological and nutritional considerations relating to the manufacture and use of the listed substance Not applicable, the request does not concern any change in the manufacturing process

Intake assessment data

(vii) 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 Not applicable, no change in any food uses is requested. Considering the intake of a substance is part of the safety evaluation routine of JECFA. We note that gellan gum had been evaluated by JECFA at its 37th and 79th session (TRS 806, TRS 990)

(viii) Estimation of dietary intakes based on food consumption data for foods in which the substance may be used. Not applicable, as no change in uses is requested. Intake assessment data are not impacted by the request for specification revision. Considering the intake of a substance is part of the safety evaluation routine of JECFA. We note that gellan gum had been evaluated by JECFA at its 37th and 79th session (TRS 806, TRS 990).

Other information (as necessary/identified)

None

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

Immediately (i.e. as of March 2018)

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:

1) **Potassium polyaspartate** used as a stabiliser in wine - safety assessment and establishment of specifications

2) **INS No 960 steviol glycosides** - revision of specifications for Rebaudioside A from Multiple Gene Donors Expressed in Yarrowia Lipolytica, FAO JECFA Monograph 19 (2016)

Enclosures:

Potassium polyaspartate

1.1 The form containing information on the request related to potassium polyaspartate (i.e. filled in Annex 2 of CL 2017/48-FA)

1.2 EFSA's safety assessment of potassium polyaspartate

1.3 Article - Toxicologic evaluation of potassium polyaspartate

INS No 960 steviol glycosides

2 The form containing information on the request related to steviol glycosides (i.e. filled in Annex 2 of CL 2017/48-FA)

Form 1.1

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	**Potassium polyaspartate**
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 a stabilizer.

1. Proposal for inclusion submitted by:

Ministero delle politiche agricole alimentari e forestali

Ministry of Agricultural Food and Forestry Policies

Directorate General of the European Union and International Policies

Italian Codex Contact Point, Via XX Settembre, 20, 00187 Roma – Italy, Phone: +39 06 46654058, Email: piue2.codex@politicheagricole.it

2. Name of substance; trade names; chemical name:

Name of substance: Potassium polyaspartate

Trade names: A-5D , Zenith

Chemical name: L-Aspartic Acid, Homopolymer, potassium salt

E number: E456

CAS number: 64723-18-8

3. Names and addresses of basic producers:

Manufacturer:

NANOCHEM SOLUTIONS, 6502 S. Archer Rd., Bedford Park IL 60501, ILLINOIS- USA

Marketer:

ESSECO S.R.L., Via San Cassiano 99, 28069 Trecate (NO) – Italy

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

NanoChem Solutions commits to provide data to support the proposal for inclusion of potassium polyaspartate in the list of substances to be evaluated by JEFCA.

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

NANOCHEM SOLUTIONS, 6502 S. Archer Rd., Bedford Park IL 60501, ILLINOIS- USA, Attn: Grace Fan, General Manager, Tel: + 17 (847) 612-7404, E Mail: lgfan@nanochems.com

6. Justification for use:

Potassium polyaspartate is a new food additive to be used as a stabilizer against tartrate crystal precipitation in wine. Thanks to its characteristics of strong effectiveness also in highly unstable wines, stability in wine over time, and absence of sensory effects, potassium polyaspartate represents an effective, environmental friendly, inexpensive, and user friendly additive for tartaric stabilization of wine.

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: 14.2.3, Grape wines

Max. use level : 100 mg/L

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))

Potassium polyaspartate is currently used in countries of the European Union (EU)

EU: food additive Regulation (EC) No 1333/2008, Annex II amended by Commission Regulation (EU) 2017/1399 of 28 July 2017

EU: oenological practices Regulation (EC) No 606/2009 Annex IA amended by the Regulation (EU) 2017/1961 of 2 August 2017

Other countries: product registration in progress / in preparation

In 2016 OIV (Organisation International de la Vigne e du Vin) adopted the Resolution OIV-Oeno-543-2016 recommending the use of potassium polyaspartate for wine stabilisation. OIV is an international intergovernmental organisation of recognised competence in international harmonisation of practices and standards in the field of vine and wine.

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

Toxicological data

The results of toxicological studies show as potassium polyaspartate is negligible absorbed, it does not affect gut cells integrity and it does not induce any activation of the immune system. It is not mutagenic or genotoxic and it does not cause any toxic effect, even in case of repeated dosing (90 days NOAEL = 1000 mg/kg body weight /day, maximum tested dose). Thus it can be concluded that the proposed use of potassium polyaspartate as food additive for tartaric stabilization in wine does not represent a safety concern.

The EFSA opinion on Potassium polyaspartate provide details on the toxicological assessment.

(i) Metabolic and pharmacokinetic studies

See EFSA scientific opinion chapter 3.3.1. Quotation:

“The Panel considered that there was negligible absorption of polyaspartate”

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

Toxicity & carcinogenicity

See EFSA scientific opinion chapter 3.3.3 and 3.3.4. Quotations:

“Based on the findings of this study, the authors report a no observed adverse effect level (NOAEL) of potassium polyaspartate (A-5D K/SD)”

“In line with the current Guidance (EFSA ANS Panel, 2012), the data from the repeated dose 90-day oral toxicity study in rats conducted with potassium polyaspartate (A-5D K/SD) and from Tier 1 toxicokinetics did not trigger additional testing for chronic toxicity and carcinogenicity.”

Reproductive toxicity, and developmental toxicity studies

see EFSA scientific opinion chapter 3.3.5. Quotation:

"In line with the current Guidance (EFSA ANS Panel, 2012), the data from the repeated dose 90-day oral toxicity study in rats conducted with potassium polyaspartate (A-5D K/SD) and from Tier 1 toxicokinetics did not trigger additional testing for reproductive and developmental toxicity."

Genotoxicity

See EFSA scientific opinion, chapter 3.3.2. Quotation:

"The Panel considered that, in line with its guidance 'In cases where all in vitro endpoints are clearly negative in adequately conducted tests, it can be concluded with reasonable certainty that the substance is not a genotoxic hazard' (EFSA ANS Panel, 2012)."

Neurotoxicity

See EFSA scientific opinion chapter 3.3.7. Quotation:

"The Panel considered that potassium polyaspartate (A-5D K/SD) has no neurotoxicity."

(iii) Epidemiological and/or clinical studies and special considerations
The relevant data from Tier 1 in vitro absorption, in vitro genotoxicity and subchronic toxicity testing performed with potassium polyaspartate showed no immunotoxicity.
No allergic reaction of sodium salt has been observed. No intolerance reactions is expected.
See also EFSA scientific opinion chapter 3.3.6.

(iv) Other data
Polyaspartic acid risk classification:

- Environmental Protection Agency: No risk reported (EPA 2012)
- International Agency for Research on Cancer: Not listed (IARC 2012)
- National Institute for Occupational Safety and Health: Not listed (NIOSH 2012)
- US Occupational Safety and Health Administration: Not regulated (OSHA 2012)

Technological data

(i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce)
Identity of the substance and structural formulae: see EFSA scientific opinion chapter 3.1.1.
Specifications: see EFSA scientific opinion chapter 3.1.2.

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

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

100 mg/L.

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

see EFSA scientific opinion chapter 3.2.2. Quotation:

"The mean dietary exposure from the proposed typical use level of 200 mg/L ranged from 0.01 to 0.2 mg/kg bw per day in adults up to 0.04 to 0.4 mg/kg bw per day in the elderly. The high-level intake ranged from 0 to 1.0 in adults and from 0.3 to 1.2 mg/kg bw per day in the elderly.

At the proposed ML of 300 mg/L, the mean dietary exposure ranged from 0.02 to 0.4 mg/kg bw per day in adults up to 0.05 to 0.6 mg/kg bw per day in the elderly. The high-level intake ranged from 0 to 1.4 in the adults and from 0.4 to 1.8 mg/kg bw per day in the elderly."

Other information (as necessary/identified)

None

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

Data is available and can be submitted when required.

Form 2

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	*INS 960 steviol glycosides (rebaudioside A and M respectively)*
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	*Request for a revision of specifications for Rebaudioside A from Multiple Gene Donors Expressed in Yarrowia Lipolytica (FAO JECFA Monograph 19 (2016)).* *The purpose is to revise the specifications (2016 Monograph) on Rebaudioside A from Multiple Gene Donors Expressed in Yarrowia by including data on Rebaudioside M and renaming the specifications as appropriate (e.g. Steviol glycosides produced by Yarrowia lipolytica).*

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 substance; trade name(s); chemical name(s):

Steviol glycosides

3. Names and addresses of basic producers:

DSM Food Specialties, PO Box 1, 2600 MA Delft, The Netherlands Tnv Dr J.A.G. van de Wiel, PP 600-0250

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):

DSM Food Specialties contact person: Jeanine van de Wiel, Jeanine.Wiel-van-de@DSM.com

6. Justification for use:

The GSFA includes provisions for steviol glycosides used as sweetener. The proposed revision of the specifications does not alter the justification which had been provided for the adopted GSFA provisions.

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 attachment

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))

≥ 95% Rebaudioside A product produced by Yarrowia lipolytica has GRAS status, has got an endorsed JECFA Monograph and is currently under evaluation by EFSA.

The ≥95 Rebaudioside M product produced by Yarrowia lipolytica will be submitted to FDA at the beginning of 2018 as well as to the EU Commission for evaluation by EFSA in the first half of 2018.

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

Toxicological data

(i) Metabolic and pharmacokinetic studies:

Not by our company but publications in Scientific literature on the same compounds Steviol glycosides available and scientific evaluations by EFSA and JECFA

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

Yes, 90-day study with actual ≥ 95% Rebaudioside M material, Ames test and Mouse Nucleus test as in vitro mutagenicity tests were performed.

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

Not by our company but plublications in scientific literature on Steviol glycosides available and have been evaluated by EFSA and JECFA

(iv) Other data: No

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, along the same lines as proposed for the DSM Rebaudioside A product that was evaluated by JECFA earlier

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

Yes, along the same lines as proposed for the DSM Rebaudioside A product that was evaluated by JECFA earlier.

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 by using the Steviol glycosides regulatory status as a sweetener in several food categories with established limits and conditions for use.

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

Yes, by using the FAIM model for the EU countries.

Other information (as necessary/identified)

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

In June 2018.

Attachment: INS960FoodCategoriesCXS_192eApril2015

JAPAN

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	Adenosine-5'-monophosphate deaminase from *Aspergillus oryzae*
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Safety evaluation and establishment of specifications.

1. Proposal for inclusion submitted by:

Japan

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

Name of substance: Adenosine-5'-monophosphate (AMP) deaminase

Trade name: Sumizyme DEA

Chemical name: AMP aminohydrolase;

3. Names and addresses of basic producers:

Shin Nihon Chemical Co., Ltd.

19-10 Showa-cho, Anjyo

Aichi 446-0063, 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):

Mr. Nobuo Okado
QA Director
Shin Nihon Chemical Co., Ltd.
19-10 Showa-cho, Anjyo
Aichi 446-0063, Japan

The manufacturer is represented by:

Ashley Roberts, Ph.D.
Intertek Scientific & Regulatory Consultancy
www.intertek.com
E-mail: ashley.roberts@intertek.com
Tel: +1 905-542-2900; Fax: +1 905-542-1011
Skype: ashley.roberts.intertek
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

6. Justification for use:

AMP deaminase from *Aspergillus oryzae* is intended for use during food and beverage processing to catalyse the hydrolytic deamination of 5'-AMP to produce inosine 5'-monophosphate (5'-IMP) in the production of nucleotide-rich foods and beverages and nucleotide-rich food ingredients, specifically nucleotide-rich vegetable or fruit pastes/purees and juices and nucleotide-rich food ingredients consisting of nucleotide-rich fish hydrolysates from fish roe/tissues and nucleotide-rich yeast extracts from yeast/yeast extracts. The technological purpose of this enzyme is to increase the content of 5'-IMP in food/beverages and in food ingredients for the purpose of imparting or enhancing flavour. IMP has flavouring properties and imparts or enhances the savoury or "umami" taste of food or food ingredients.

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 products, food categories, and use levels that AMP deaminase from *Aspergillus oryzae* is intended to be used are outlined in the table below.

The use of AMP deaminase from *Aspergillus oryzae* in the processing of nucleotide-rich fish hydrolysates and yeast extracts can, in turn, be added to a wide range of foods. These foods include, but are not limited to, breads, cakes, cookies, yoghurts, fresh cream, Ganache, Asian-style sauces (sesame paste, noodle sauce), soups, ice-cream, and custard products. In these instances, the nucleotide-rich ingredients are added to foods at maximum use levels not exceeding 0.2% (equivalent to 2 g/kg food). Accordingly, the maximum levels that could potentially be present in final foods containing nucleotide-rich ingredients prepared with the enzyme are minimal (i.e., not exceeding 0.17 mg TOS/kg food). This amount is much less than those that could potentially occur from the use of AMP deaminase from *Aspergillus oryzae* in the processing of foods that are directly consumed (i.e., 85.6 mg TOS/kg food), such as nucleotide-rich vegetable or fruit pastes/purées and juices.

GSFA Food Category	Food	Maximum Use Level (mg TOS/kg)
04.1.2.8 Fruit preparations, including pulp, purees, fruit toppings and coconut milk	Fruit pastes and purees	85.6
04.2.2.5 Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed purees and spreads (e.g. peanut butter)	Vegetable purees	85.6
04.2.2.6 Vegetable (including mushrooms and fungi, roots and tubers, pulses and legumes, and aloe vera), seaweed, and nut and seed pulps and preparations (e.g. vegetable desserts and sauces, candied vegetables) other than food category 04.2.2.5	Vegetable pastes	85.6
12.6.4 Clear sauces (e.g. fish sauce)	Fish sauce	85.6
12.8 Yeast and like products	Yeast extract	85.6
14.1.2.1 Fruit juice	Fruit juice	85.6
14.1.2.3 Concentrates for fruit juice	Fruit juice concentrates	85.6

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 country(ies))

AMP deaminase from *Aspergillus oryzae* is currently authorised for use as a food additive in Japan and has been commercially marketed since 2007.

AMP deaminase derived from *Aspergillus melleus* and *Streptomyces murinus* are currently marketed for use in food processing in the European Union (EU) according to the Association of Manufacturers and Formulators of Enzyme Products (AMFEP). In China, AMP deaminase from *A. melleus* is currently permitted for use in food processing (uses not specified) as listed in the National Standard on Food Safety – Standard for Use of Food Additives GB 2760-2011.

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 toxicological data on AMP deaminase from *Aspergillus oryzae* are available and can be provided upon request. Briefly, the data includes a bacterial reverse mutation test and an *in vitro* mammalian chromosomal aberration test, and a repeated-dose 90-day oral toxicity study in rats. All tests were conducted in compliance with the Organisation of Economic Co-operation and Development (OECD) Principles of Good Laboratory Practice (GLP) and in accordance with the respective OECD Guidelines for the Testing of Chemicals.

Data to support the non-pathogenicity, non-toxigenicity, and history of safe use of the production strain are also available and can be provided upon request.

Technological data

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

A specification of AMP deaminase from *Aspergillus oryzae* 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 requirements for enzyme preparations in the Food Chemicals Codex, 10th edition.

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

AMP deaminase from *Aspergillus oryzae* is intended to be used in food and beverage processing for the purpose of increasing the content of 5'-IMP in food/beverages and in food ingredients to impart or enhance flavour. IMP has flavouring properties and imparts or enhances the savoury or "umami" taste of food or food ingredients. The deaminase has a minimum shelf-life of 12 months when stored at 20 to 25°C under dry conditions in the original packaging. Its thermostability and pH-stability have been determined to be relatively stable at temperatures of 0 to 55°C and pH 5.0 to 7.0.

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 maximum level of the enzyme preparation to be added during food processing on a total organic solids (TOS) basis is 85.6 mg TOS/kg food substrate. The enzyme preparation will be used only at the level required to achieve the intended effect (i.e., *quantum satis*).

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

Estimation of the dietary intakes of AMP deaminase from *Aspergillus oryzae* has been made in the EU and United States using the budget method. The theoretical maximum daily intake of the enzyme is shown in the table below.

Category	**Maximum Use Level (mg TOS/kg)**	**Total exposure (mg TOS/kg bw/day)**
Solid foods	85.6	0.54[a]
Non-milk beverages	85.6	2.14[b]
Total food and beverage		2.68

[a] Calculated using the level of consumption of solid foods (0.05 kg/kg bw/day), proportion of solid foods containing AMP deaminase from *Aspergillus oryzae* (12.5%), and the maximum use level (85.6 mg TOS/kg food).

[b] Calculated using the level of consumption of non-milk beverages (0.1 kg/kg bw/day), proportion of non-milk beverages containing AMP deaminase from *Aspergillus oryzae* (25%), and the maximum use level (85.6 mg TOS/kg food).

Other information (as necessary/identified)

Other necessary information as identified by JECFA can be provided upon request.

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

Immediately

SUDAN

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	Gum Arabic: Acacia seyal and Acacia senegal
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Revaluation add new functional use of GUM Arabic as a source of natural prebiotic in the existing specification of Gum Arab 1999

1. Proposal for inclusion submitted by: Sudan

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

Name of Substance: Gum Arabic

Trade Name: Hashab /Safast/ pre-bio C/Talh/Sweet/Fiber/Pre-bio D

Chemical name: Acacia seyal and Acacia sengal

3. Names and addresses of basic producers:

Dar Savanna Ltd, Block 24, St.37, Khartoum 2, Khartoum, Sudan

Perfect life, Algoz3 industrial Area, Dubai UAE

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. Isam Sidig Ahmed, email: I.sidig@prebiotica@.com

***6.* Justification for use**: Boost increase of good probiotic bacteria; confer health benefits and Source of mineral like calcium

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):

Daily Juice Confectionary Cereals natural rich source of pre-biotic (10-15g/day)

8. Is the substance currently used in food that is legally traded in more than one country? Yes,

(please identify the countries); or, has the substance been approved for use in food in one or more country? (please identify the country(ies))

Sudan, UAE, Qatar, Kuwait, Malaysia, USA, Holland and China, Approved for use as source of pre-biotic and as ingredient.

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 √ available

(iv) Other 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) √ available

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

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

December 2018

Supporting documents

EU SPECIALTY FOOD INGREDIENTS

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	*Steviol glycosides*
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	*Can JECFA revise its 2016 Monograph on Rebaudioside A produced by Yarrowia lipolytica including the data on Rebaudioside M and rename the Monograph to Steviol glycosides produced by Yarrowia lipolytica.*

1. Proposal for inclusion submitted by: EU Specialty Food Ingredients

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

3. Names and addresses of basic producers:

DSM Food Specialties, PO Box 1, 2600 MA Delft, The Netherlands Tnv Dr J.A.G. van de Wiel, PP 600-0250

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):

DSM Food Specialties contact person: Jeanine van de Wiel, Jeanine.Wiel-van-de@DSM.com

6. Justification for use: sweetener

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 attachment

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))

≥ 95% Rebaudioside A product produced by Yarrowia lipolytica has GRAS status, has got an endorsed JECFA Monograph and is currently under evaluation by EFSA. The ≥95 Rebaudioside M product produced by Yarrowia lipolytica will be submitted to FDA start of 2018 and successively to EU Commission for evaluation by EFSA in the first half of 2018.

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

Toxicological data

(i) Metabolic and pharmacokinetic studies:

Not by the manufacturer but publications in Scientific literature on the same compounds Steviol glycosides available and scientific evaluations by EFSA and JECFA.

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

Yes, 90-day study with actual ≥ 95% Rebaudioside M material, Ames test and Mouse Nucleus test as in vitro mutagenicity tests were performed.

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

Not by the manufacturer but publications in scientific literature on Steviol glycosides available and have been evaluated by EFSA and JECFA.

(iv) Other data:

No

Technological data

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

Yes, along the same lines as proposed for the DSM Rebaudioside A product that was evaluated by JECFA earlier

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

Yes, along the same lines as proposed for the DSM Rebaudioside A product that was evaluated by JECFA earlier.

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.

Yes by using the Steviol glycosides regulatory status as a sweetener in several food categories with established limits and conditions for use.

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

Yes, by using the FAIM model for the EU countries.

Other information (as necessary/identified)

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

June 2018.

Attachment: INS960FoodCategoriesCXS_192eApril2015

INTERNATIONAL ASSOCIATION OF COLOR MANUFACTURERS (IACM)

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	Black carrot 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 specification for use as a color.

1. Proposal for inclusion submitted by:

International Association of Color Manufacturers (IACM)

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

3. Names and addresses of basic producers: San Joaquin Valley Concentrates, 5631 E Olive Ave, Fresno, CA 93727

4. Has the manufacturer made a commitment to provide data? IACM or its member companies will provide the available 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, scodrea@iacmcolor.org.

6. Justification for use: Use 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):

Among the food products and food categories which we anticipate providing to JECFA for consideration are beverages (14.0), cereals and cereal products (6.0), hard candy (5.2.1), soft candy (5.2.2), chewing gum (5.3) and dairy products (1.0). For hard candy (5.2.1), soft candy (5.2.2.), use levels are not expected to exceed 1.0%, for chewing gum (5.3.), use levels should not exceed 2% (dependent on color strength of the extract). Additional food category and use level information will be provided later.

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))

Black Carrot Extract is an anthocyanin-based vegetable juice color and is allowed under the group color name “Anthocyanins” (E163) in Australia, Canada, the European Union, Malaysia, New Zealand, Russia, Turkey and Ukraine. It is also approved for use under “Vegetable juice” color regulations in Japan, Singapore and the United States. Specifically, it was also approved as “Black Carrot Extract” this past year in the Republic of Korea as coloring for use in candies.

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

Toxicological data

(i) Metabolic and pharmacokinetic studies

Charron CS et al. Bioavailablity of Anthocyanins from Purple Carrot Juice: Effects of Acylation and Plant Matirix. *J Agric Food Chem*., 2009. 57(4):1226-30

Kay CD et al. Anthocyanins and Flavanones are more bioavailable than Previously Perceived: A Review of Recent Evidence. *Annual Review of Food Science and Technology*, 2017, 8:155-180.

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

studies in animals and genotoxicity studies

Pourrat H, Bastide P, Dorier P and Tronche P. Préparation et activité thérapeutique de quelques glycosides d'anthocyanes. *Chim. Thérap*, 1967, 2: 33-38 (as referred to by JECFA, 1982).

(iii) Metabolic and pharmacokinetic studies

Czank C, Cassidy K, Zhang Q, Kay CD. Human Metabolism and Elimination of the Anthocyanin, Cyanidin-3-glucoside: A 13C-Tracer Study. *Am. J. of Clinical Nutrition,* 2013, 97: 995-1003.

De Ferrars RM, *et al.*, The Pharmacokinetics of Anthocyanins and their Metabolites in Humans.*Br J. Pharmacol,* 2014, 171:3268-82.

Del Rio D, Rodriguez-Mateos AM, Spencer JPE, Tognolini M, Borges G, Crozier A. Dietary (poly)phenolics in Human Health and Disease, Bioavailability, Evidence of Protective Effects, and Potential Mechanisms. 18 *Antioxid. Redox Signal*, 2013 18(14): 1818-92.

Fang J. Bioavailability of Anthocyanins. 46 *Drug Metabolism Review,* 2014, 46(4): 508-20.

Matsumoto H, Inaba H, Kishi M, Tominaga S ,Hirayama M, and Tsuda T. Orally administered Delphinidin 3-Rutinoside and Cyanidin 3-Rutinoside are directly absorbed in rats and humans and appear in the blood as the intact forms. *J. of Agric. and Food Chem*, 2001, 49:1546-51.

McGhie TK, Walton MC, The Bioavailability and Absorption of Anthocyanins: Towards A Better Understanding. *Molecular Nutrition and Food Research,* 2007, 51(6): 702-13.

Mertens-Talcott SU, Rios J, Jilma-Stohlawetz P, Pacheco-Palencia LA, Meibohm B, Talcott ST, Derendorf H. Pharmacokinetics of Anthocyanins and Antioxidant Effects After the Consumption of Anthocyanin-rich Acai Juice and Pulp (Euterpe oleracea Mart.) in Human Healthy Volunteers. *J Agric. Food Chem*, 2008, 17: 7796-02.

Rodriguez-Mateos A, Vauzour D, Kreuger CG, Shammuganayagam D, Reed J, *et al.*, Flavanoids and Related Compounds, Bioavailability, Bioactivity and Impact on Human Health: An Update. *Arch Toxicol,* 2014, 88(10): 1803-53.

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

Glei M, *et al.,* Initial in vitro Toxicity Testing of Functional Foods Rich in Catechins and Anthocyanins in Human Cells. *Toxicology In Vitro,* 2003,17(5-6): 723-29.

Haveland-Smith RB. Evaluation of the genotoxicity of some natural food colors using bacterial assays. *Mutation Research*, 1987, 91:285-290 (as referred to by JECFA, 1982).

Inoue K, Morikawa T, Takahashi N, Yoshida N, Ogawa K. A 13-week Study of Grape Skin Extract in F344 Rats. *J. Toxicol Sci*., 2013, 38(4): 559-70.

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

Liu C, Sun J, Lu Y, Bo Y. Effects of Anthocyanin on Serum Lipids in Dyslipidemia Patients: A Systematic Review and Meta-Analysis. *PLoS ONE,* 2016, 11(9): e0162089*.*

(vi) Other data

Degirmenci H, Karapinar M, Karabiyikli S. The survival of E. coli O157:H7, S. Typhimurium and L. monocytogenes in black carrot juice, *International Journal of Food Microbiology,* 2012, 153 (1-2): 212-5.

Technological data

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

Black carrot extract is expressed from fresh, mature purple carrot (daucus carota) plant. The primary coloring pigments in black carrot are comprised of anthocyanins. The coloring principle in the black carrot color consists primarily of the cyanidin group of anthocyanins. The common acids in black carrot anthocyanins are coumaric, ferulic, and sinapic acids. Due to natural variations in crops, small seasonal variations are expected to occur. Further specifications will be provided to JECFA upon call for data.

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

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

To be provided to JECFA upon inclusion in call for data.

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

Black carrots, which are used to create the extract, are commonly consumed as part of the global diet. Data collected from 2007 to 2010 by the US National Health and Nutrition Examination Survey (NHANES) and Wu et al will be provided.

References:

What We Eat in America, NHANES 2007-2010, Table 1a ("Flavonoids from food and beverages –overall total and anthocyanidins, available at:
https://www.ars.usda.gov/ARSUserFiles/80400530/pdf/0710/Table_1_FLAV_GEN_0710.pdf

Wu X, Beecher GR, Holden JM, et al. Concentrations of Anthocyanins in Common Foods in the United States and Estimation of Normal Consumption. *J. of Agric. and Food Chem.,* 2006, 54(11): 4069–75.

Other information (as necessary/identified)

Algarra, M, Fernandes A, Mateus N, de Freitas V, da Silva JC and Casado J. Anthocyanin profile and antioxidant capacity of black carrots (Daucus carota L. spp sativus var. atrorubens Alef) from Cuevas Baja, Spain. *Food Composition and Analysis, 2014, 33: 71-76.*

Assous MT, Abdel-Hardy MM and Medany GM. Evaluation of red pigment extracted from purple carrots and its utilization as antioxidant and natural food colorants. *Annals Agricultural Science,* 2014, 59, 1-7.

Azuma K, Ohyama A, Ippoushi K, Ichiyanagi T, Takeuchi A, Saito T, Fukuoka H. Structures and Antioxidant Activity of Anthocyanins in Many Accessions of Eggplant and its Related Species. *J Agric Food Chem*, 2008, 21: 10154-59.

Bowen-Forbes CS, Zhang Y, Nair MG, Anthocyanin Content, Antioxidant, Anti-Inflammatory and Anticancer Properties of Blackberry and Raspberry Fruits. *J. Food Composition and Analysis*, 2010, 23(6): 554–56.

Claudio SR, Gollucke AP, Yamamura H, Morais DR, Bataglion GA, Eberlin MN, Peres RC, Oshima CT and Ribeiro DA. Purple carrot extract protects against cadmium intoxication in multiple organs of rats: genotoxicity, oxidative stress and tissue morphology analyses. *J. Trace Elem. Med. Biol., 2016, 33:37-47.*

Curtis PJ, Kroon PA, Hollans WJ, Walls R, Jenkins G, Kay CD, Cassidy A. Cardiovascular disease risk biomarkers and liver and kidney function are not altered in postmenopausal women after ingesting an elderberry extract rich in anthocyanins for 12 weeks. *J. Nutr*., 2009, 139(12):2266-2271.

Kammerer D, Carle R and Shieber A. Quantification of anthocyanins in black carrot extracts (Daucus carota ssp. Sativus var. atrorubens alef) and evaluation of their color properties. *European Food Research and Technology,* 2004, 219:479–486.

Muñoz-Espada AC, Wood KV, Bordelon B, *et al.* Anthocyanin Quantification and Radical Scavenging Capacity of Concord, Norton, and Marechal Foch Grapes and Wines. *J. of Agric. and Food Chem.* , 2004, 52(22): 6779–86.

Siriwoharn T, Wrolstad RE, Finn CE, et al., Influence of Cultivar, Maturity, and Sampling on Blackberry (Rubus L. Hybrids) Anthocyanins, Polyphenolics, and Antioxidant Properties. *J. of Agric. and Food Chem*, 2004, 52(26): 8021–30.

Wright OR, Netzel GA and Sakzewsji AR. A randomized, double-blind, placebo-controlled trial of the effect of dried purple carrot on body mass, lipids, blood pressure, body composition, and inflammatory markers in overweight and obese adults.: the QUENCH trial. Can. *J. Physiol. Pharmacol.,* 2013, 91:480-488.

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

IACM or its member companies can submit this data by December 2018.

THE INTERNATIONAL COUNCIL OF BEVERAGES ASSOCIATIONS (ICBA)

As concluded at CCFA49, the International Council of Beverages Associations (ICBA) is pleased to present its research plan to fulfill CCFA's request. "**[A]t CCFA50, industry would confirm their commitment and indicate the deadline for the submission of the data to JECFA**… Committee agreed to keep the maximum level of benzoate in FC 14.1.4 at 250 mg/kg with Note 13 and to revise the Note 301 to read "*interim* maximum level until CCFA50". (para. 72, REP17/FA) "The JECFA Secretariat further clarified that … the industry sector (*shall*) provide general input on additional toxicological testing, taking animal health and welfare and other relevant issues into account." (para. 68, REP17/FA) ICBA's research proposal along with recently completed research applicable to the safe use of benzoate food additives are included herein and below.

In view of JECFA's interest in early-life exposure (i.e., the children/adolescent population) (as noted at the 80th JECFA meeting and the CCFA48) and inherent limitations associated with the 1960 Kieckebusch and Lang four-generational rodent study in establishing the benzoate point of departure (POD) (i.e., as the 1960 study did not provide for a dose-response curve in that the highest dose tested did not have a response), [1] three toxicology experts in different regions (U.S.A., Canada and U.K.) were tasked with reviewing existing summaries on benzoate toxicity and providing their testing recommendations to fulfill CCFA's request. Those summaries reviewed included: 1996 JECFA benzoate toxicological assessment, [2] 2000 WHO Concise International Chemical Assessment Document (CICAD) 26,[3] 2001 cosmetic assessment of benzoates[4] and the 2016 European Food Safety Authority (EFSA) scientific opinion on benzoates.[5] Replacing the pivotal 1960 multi-generational reproductive toxicity study with an updated OECD 443 protocol extended one-generation repro-developmental study was suggested as a possible basis to revise the benzoate POD.

In addition to the new toxicological evaluation (to initiate early 2018), the feasibility of reducing default uncertainty factors - based on the existing comprehensive human and rodent dataset for benzoic acid – was considered and possible refinement to intake assessment assumptions was investigated due to possible ADI exceedance (as reported by JECFA and to respond to a CCFA48 request to justify the safety of suggested benzoate use levels for beverages FC 14.1.4 - JECFA80, REP16/FA.) The findings suggest the ADI could be increased two-fold based on the possible reduction of the default interspecies toxicokinetic uncertainty factor of at least two-fold and the updated intake estimates in the four higher-consuming markets were below the ADI. Each investigative effort has since been published and accessible below:

- Gradient benzoate pharmacokinetic and pharmacodynamic uncertainty factors literature review - Zu, K., D.M. Pizzurro, T.A. Lewandowski and J.E. Goodman. 2017. Pharmacokinetic Data Reduce Uncertainty Regarding the Acceptable Daily Intake for Benzoic Acid and Its Salts. *Regulatory Toxicology and Pharmacology*. 89: 83-94.

- Colorado State University Benzoate physiologically-based pharmacokinetic (PBPK) modeling - Hoffman, T.E., and W.H. Hanneman. 2017. Physiologically-Based Pharmacokinetic Analysis of Benzoic Acid in Rats, Guinea Pigs and Humans: Implications for Dietary Exposures and Interspecies Uncertainty. *Computational Toxicology*. 3: 19-32.

- Intertek Benzoate intake assessment - Martyn, D.M., A.A. Lau, M.N. Darch and A.S. Roberts. 2017. Benzoates intakes from non-alcoholic beverages in Brazil, Canada, Mexico and the United States. *Food Additives and Contaminants Part A*. 34(9): 1485-1499.

Thus, as agreed to at CCFA49, ICBA[6]/ is confirming its commitment to new toxicological evaluation of benzoates – i.e., performing an extended OECD protocol one-generational repro-toxicity (EOGRT) study preceded by a dose-range finding study. We anticipate that the toxicity testing will be completed by Summer 2020, in time for a JECFA re-review of not only the updated reproductive toxicity study outcomes but also of the updated analyses on possible reductions of benzoate's chemical-specific adjustment factors, default uncertainty factors and intake assumptions. ICBA also requests that CCFA50 extend the timeframe for an *interim* level of 250 ppm (as benzoic acid) for the beverage category 14.1.4. to CCFA53 when discussion on appropriate use levels for benzoates in beverages should resume based on JECFA's anticipated re-evaluation summer 2020.

[1]Kieckebusch W, Lang K. [The tolerability of benzoic acid in chronic feeding experiments]. Arzneimittelforschung. 1960 Dec;10:1001-3.
[2]Vavasour, E. JECFA (1996). BENZYL ACETATE, BENZYL ALCOHOL, BENZALDEHYDE, AND BENZOIC ACID AND ITS SALTS.
[3]2000 UNEP/ILO/WHO. Concise International Chemical Assessment Document (CICAD) 26. BENZOIC ACID AND SODIUM BENZOATE.
[4]Nair, B. 2001. Final report on the safety assessment of Benzyl Alcohol, Benzoic Acid, and Sodium Benzoate. *International Journal of Toxicology*, 20(Suppl. 3):23–50
[5]EFSA Panel on Food Additives and Nutrient Sources (ANS). Scientific Opinion on the re-evaluation of benzoic acid (E 210), sodium benzoate (E 211), potassium benzoate (E 212) and calcium benzoate (E 213) as food additives. EFSA Journal 2016. 14(3):4433.
[6]The International Council of Beverages Associations (ICBA) represents the interests of the worldwide non-alcoholic beverage industry. ICBA members include national and regional beverage associations and international beverage companies that operate in more than 200 countries and territories and produce, distribute and sell a variety of non-alcoholic sparkling (carbonated) and still (non-carbonated) beverages including soft drinks, sports drinks, energy drinks, bottled waters, flavored and/or enhanced waters, ready-to-drink teas and coffees, 100% fruit or vegetable juices, nectars and juice drinks, and dairy-based beverages.

Annex 2 – **Form for the submission of substances to be evaluated by JECFA**

Name of Substance(s)	Benzoic Acid and Its Salts
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluation)*	Re-evaluate the safety and dietary intake of benzoates based on new data: 1) the outcome of the planned extended one-generational reproduction toxicity study (OECD 443); 2) the published findings relative to benzoate's chemical-specific adjustment factors and default uncertainty factors; and 3) the published findings on new more refined dietary intake assessments. The new data to be provided will consist of: • Study outcomes from the dose-range finding study (according to OECD 422) and from the Extended One Generation Reproductive Toxicity Study (according to OECD 443); • Human clinical data on sodium benzoates demonstrating similar pharmacokinetics between humans and rats, supporting an adjustment to the chemical-specific adjustment factors for benzoates, and, consequently to the ADI (published); • Physiologically-based pharmacokinetic (PBPK) modeling further supporting reductions in default uncertainty factors (published); and, • Highly refined intake assessment reflective of actual uses weighted according to market volume data to ensure quantitative representativeness for corresponding beverage types (published).

1. Proposal for inclusion submitted by:

Katherine Loatman, Executive Director (1 202.321.3085), International Council of Beverages Associations

E-mail: Kate@icba-net.org

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

Substance: Benzoic acid and its salts

Trade Name: N/A

Chemical Name(s):

Benzoic acid, benzenecarboxylic acid, phenylcarboxylic acid (CAS number 65-85-0)

Sodium benzoate, sodium salt of benzenecarboxylic acid, sodium salt of phenylcarboxylic acid (CAS number 532-32-1)

Potassium benzoate, potassium salt of benzenecarboxylic acid, potassium salt of phenylcarboxylic acid (CAS number 582-25-2 (anhydrous))

3. Names and addresses of basic producers:

Manufacturers may be contacted through Katherine Loatman of ICBA.

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

The International Council of Beverages Associations (ICBA) members on behalf of the beverage industry are committed to carrying out the extended one-generational reproductive toxicity testing (EOGRT Study, OECD 443). The beverage industry has already completed and published study findings relative to benzoate's chemical-specific adjustment factor, default uncertainty factors and intake assessment assumptions, as noted above. These will likewise be made available for JECFA's consideration.

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

Extended One Generational Reproductive Toxicity Study:
Prägati Sawhney Coder, Ph.D., DABT, Director, Developmental and Reproductive Toxicology
Charles River
1407 George Road, Ashland, OH 44805
P: 419.289.8700
pragati.coder@crl.com

Chemical-Specific Adjustment Factors:
Julie E. Goodman, Ph.D., DABT, FACE, ATS, Principal
Gradient
20 University Road
Cambridge, MA 02138
617-395-5525
JGoodman@gradientcorp.com

PBPK Default Uncertainty Factors:
William Hanneman, Ph.D.
Center for Environmental Medicine, Colorado State University
Fort Collins, Colorado
(970) 491-5652
William.Hanneman@colostate.edu

Dietary Intake Assessment:
Ashley Roberts, Ph.D.
Intertek Scientific & Regulatory Consultancy
2233 Argentia Road, Suite 201
Mississauga, Ontario, Canada
L5N 2X7
905-542-2900
ashley.roberts@intertek.com
www.intertek.com

6. Justification for use:

The use of benzoates is advantageous in beverage products and technologically justified to ensure preservation of beverage quality, enhanced beverage shelf-life and reduction in yeast, molds and bacterial growth.

Intrinsic, extrinsic and process-related factors affect susceptibility of water-based flavored drinks to microbial growth. In commercial practice, water-based flavored drinks may spoil and are rendered unappealing or unpalatable by the growth of various fungi and acid tolerant bacteria. Microbiological activity can occur in “still” and “sparkling” (carbonated) beverages, as well as in concentrates. In order to prevent undesirable microbiologically induced changes, manufacturers rely on sophisticated preservation systems that include the appropriate use of antimicrobials such as benzoic acid or its salts (benzoates).

The need for benzoates is determined by beverage matrix, processing, packaging and storage conditions and the ubiquitous microflora of the environment, containers and ingredients. As pH increases, the amount of benzoic acid (i.e., the active form of benzoates) in beverages decreases resulting in higher minimum inhibitory concentrations (MIC) to achieve the same functionality. A beverage with pH 4.3 and 500 ppm of benzoic acid has approximately the same amount of undissociated benzoic acid (active form) as a beverage at pH 3.5 with 250 ppm of benzoic acid.

When used at effective levels, benzoates maintain the quality, stability and integrity of beverages as part of a multi-component multi-hurdle preservative system. Benzoates often are effective against organisms that are otherwise tolerant to other antimicrobial agents and vice versa.

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):

14.1.4 Water-based flavoured drinks, including “sport,” “energy,” or “electrolyte” drinks and particulated drinks

Maximum use of benzoates at a level of 250 mg/kg as benzoic acid as consumed in food category 14.1.4 with footnote Note 127 “On the served to the consumer basis” and an additional footnote that reads “Except for use in beverages with pH greater than 3.5 at 500 mg/kg as consumed”.

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).

Australia, Brazil, Canada, China, European Union, India, Iran, Japan, Mexico, New Zealand, Philippines, South Africa, South Korea, Thailand, United States of America, etc.

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

Toxicological data

(i) Metabolic and pharmacokinetic studies – X – YES

(ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies – To be made available by December 2019 for the JECFA 2020 Summer meeting (timeline attached)

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

(iv) Other data (available now)

X -Literature review of benzoate-related chemical specific adjustment factors

X- PBPK modeling

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

***Intake assessment data* (available now)**

(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

X (brand-specific for identified beverage types in Brazil, Canada, Mexico and U.S.A.)

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

X (based on WHO's individual food approach - please see ICBA comments in response to CCFA 49th Agenda Item 5(a) General Standard for Food Additives (GSFA): provisions for benzoates in FC 14.1.4. … - CX/FA 17/49/7 Appendix 3.)

Other information (as necessary/identified) (available now)

X – Brand-specific market volume data to seek quantitative "representativeness" weighting for levels utilized in the assessment.

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

December 2019 (Timeline for the EOGRT Study Attached)

ICBA thanks Codex members for taking these comments into consideration. Any questions on this matter should be directed to Dr. Maia Jack, vice president of science and regulatory affairs at the American Beverage Association (mjack@ameribev.org; 202-463-6756).

Supporting documents

INTERNATIONAL ORGANIZATION OF THE FLAVOR INDUSTRY (IOFI)

This is in response to the CL 2017/48-FA (April 2017): Request for information and comments on the priority list of substances proposed for evaluation by JECFA. On behalf of the International Organization of the Flavor Industry (IOFI), we provide the following comments for consideration at the forthcoming 50th Session of the Codex Committee on Food Additives.

IOFI respectfully requests the addition of 8 previously evaluated flavouring agents to the JECFA Priority List in support of updating the specifications. The required information for the flavouring agents as requested in Annex 2 of CL 2017/48-FA is attached as Annex2_2017CCFA50. The flavouring agents listed in annex III the most recent specifications evaluation by JECFA and a brief description of the nature of the update.

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	See Appendix II for list of proposed substances
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	Do the published specifications for the flavouring agents as listed in Annex 3 represent what is in global commerce? *Data have been presented to IOFI that update specific specifications values and identifiers submitted previously.*

1. Proposal for inclusion submitted by:

International Organization of the Flavor Industry

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

List of 8 flavouring agents (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 Flavor 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 previously 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, Latin America and Japan)

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

Toxicological data

(i) Metabolic and pharmacokinetic studies Previously submitted

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

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

(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 Previously submitted

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

Other information (as necessary/identified)

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

December 01, 2018

Annex 3 - Priority list of compounds proposed for specifications modification by JECFA Priority List to be considered at the 50th session of the Codex Committee on Food Additives

History	FEMA No	JECFA No	CAS	Principle Name	Most recent Specification Evaluation	Status	Issue
Old	3107	889	121-33-5	Vanillin	2001 (Session 57)	Full	Change of m.p.
Old	2464	893	121-32-4	Ethyl vanillin	2001 (Session 57)	Full	Change of m.p.
Old	3639	979	432-25-7	2,6,6-Trimethyl-1&2-cyclohexen-1-carboxaldehyde	2002 (Session 59)	Full	Inclusion of second CAS no.
Old	3773	1029	13794-15-5	Sodium 2-(4-methoxyphenoxy)propanoate	2002 (Session 59)	Full	Inclusion of second CAS no.
Old	3592	967	4501-58-0	2,2,3-Trimethylcyclopent-3-en-1-yl acetaldehyde	2002 (Session 59)	Full	Assay value >95% (mixture)
Old	2450	345	111-62-6	Ethyl oleate	1998 (Session 51)	Full	Named flavouring agent is >85% with secondary components in the sum of linoleic and stearic acids <15%.
Old	3735	1236	7392-19-0	2,2,6-Trimethyl-6-vinyltetrahydropyran	2003 (Session 61)	Full	Assay value of material in commerce >95%
Old	3509	547	54957-02-7	alpha-methyl-beta-hydroxypropyl alpha-methyl-beta-mercaptopropyl sulfide	1999 (Session 53)	Full	Assay value of material in commerce >95%

INTERNATIONAL STEVIA COUNCIL (ISC)

The International Stevia Council (ISC) is submitting a notification (in attachment) for the submission of substances to be evaluated by JECFA in response to the Circular Letter CL 2017/48-FA of April 2017.

The attached notification aims at asking JECFA to prepare stand-alone JECFA specification monographs for steviol glycosides that are produced through technologies outside of the current specification for steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni and to confirm that the glycosides produced through these technologies are covered by the current steviol glycoside ADI.

These technologies include:

a) fermentation involving the use of genetically modified (GM) microorganisms in the production of steviol glycoside preparations with high levels of a specific rebaudioside such as Rebaudioside M or for example, the JECFA specification for rebaudioside A produced from gene donors expressed in *Yarrowia lipolytica* (2016);

b) Bioconversion, whereupon steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni are enzymatically converted to products containing higher percentages of singular steviol glycosides such as rebaudioside D and M, using isolated purified enzymes generated from (GM) sources, and

c) Enzyme modified or glucosylated steviol glycosides, whereupon steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni are enzymatically modified to larger steviol glycosides using an enzyme system from a non-GM or GM source.

FORM FOR THE SUBMISSION OF SUBSTANCES TO BE EVALUATED BY JECFA

In completing this form, only brief information is required. The form may be retyped if more space is needed under any one heading provided that the general format is maintained.

Name of Substance(s):	
Question(s) to be answered by JECFA *(Provide a brief justification of the request in case of re-evaluations)*	To prepare stand-alone JECFA specification monographs for steviol glycosides that are produced through technologies outside of the current specification for steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni and to confirm that the glycosides produced through these technologies are covered by the current steviol glycoside ADI. These technologies include, a) fermentation involving the use of genetically modified (GM) microorganisms in the production of steviol glycoside preparations with high levels of a specific rebaudioside such as Rebaudioside M or for example, the JECFA specification for rebaudioside A produced from gene donors expressed in *Yarrowia lipolytica* (2016); b) Bioconversion, whereupon steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni are enzymatically converted to products containing higher percentages of singular steviol glycosides such as rebaudioside D and M, using isolated purified enzymes generated from (GM) sources, and c) Enzyme modified or glucosylated steviol glycosides, whereupon steviol glycosides extracted from the plant *Stevia rebaudiana* Bertoni are enzymatically modified to larger steviol glycosides using an enzyme system from a non-GM or GM source. Both the fermentation and bioconversion products are identical to steviol glycosides found in the stevia leaf. The enzyme modified products typically contain steviol glycoside components that occur naturally in the plant and some components that may not occur naturally in the plant.

1. Proposal for inclusion submitted by:

International Stevia Council

Maria Teresa Scardigli, Executive Director, International Stevia Council, Global Office, Avenue Jules Bordet 142, 1140 – Brussels, Belgium

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

Steviol Glycosides, Rebaudioside A, Rebaudioside D, Rebaudioside M; Enzyme Modified Steviol Glycosides, Enzyme Modified Stevia Leaf Extract

3. Names and addresses of basic producers:

Blue California, 30111 Tomas, Rancho Santa Margarita CA , U.S.A. 92688

Cargill Incorporated, 15407 McGinty Road West, M.S. 163, Wayzata, MN, USA 55391

DSM Food Specialties, PP602-8250 PO Box 1, 2600 MA Delft, The Netherlands

PureCircle Limited, 915 Harger Road, Suite 250, Oak Brook, Illinois, 60523 U.S.A.

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

All 4 manufactures have made a commitment to provide the requested data.

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

Hadi Omrani, Manager – Technical & Regulatory Affairs, Blue California, 30111 Tomas, Rancho Santa Margarita, CA, U.S.A. 92688

Nicole Cuellar-Kingston, Principal Scientist, Scientific & Regulatory Affairs, Cargill Incorporated, 15407 McGinty Road West, M.S. 163, Wayzata, MN, USA 55391

Jeanine A. G. van de Wiel, Global Regulatory Affairs, Group Leader, DSM Food Specialties, PP602-8250 PO Box 1, 2600 MA Delft, The Netherlands

Sidd Pukayastha PhD, VP, Head of Global Scientific & Regulatory Affairs, PureCircle Limited, 915 Harger Road, Suite 250, Oak Brook, Illinois, 60523 U.S.A.

6. Justification for use:

An amendment to the current JECFA specifications is justified based upon the commercial availability of a number of steviol glycoside preparations that contain for example a high proportion of singular steviol glycosides such as rebaudiosides A, D or M from fermentation or bioconversion and glycosides containing additional glucose units that are produced through enzyme modification.

In addition to DSM's high purity rebaudioside A material produced *via* fermentation from a genetically modified *Yarrowia lipolytica*, Cargill manufactures a high purity reabaudisode D or M product using a similar fermentation process using *Saccharomyces cerevisiae* expressing steviol glycoside biosynthesis pathway genes. Furthermore, Blue California manufactures either a high purity rebaudioside D or M product using GM strains of *Pichia pastoris*, expressing the enzymes UDP glucosyltransferase and sucrose synthase. These enzymes convert both rebaudioside A and other steviol glycosides to highly pure rebaudioside D or M products. A number of companies including PureCircle Limited also produce enzyme modified or glucosylated steviol glycoside preparations where the starting material is a purified stevia rebaudioside plant extract that meets the current JECFA specification. However, in this case, the plant extracts are enzymatically modified such that additional glucose moieties are conjugated to the parent steviol glycoside structure *via* a-(1-4) linkages. These reactions generate a mixture of glycosylated steviol glycosides containing from 1 to 20 additional bound glucose units.

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):

There is no requirement to amend the existing provision of food products, food categories and use levels previously adopted for steviol glycosides. The current GSFA SG listing will therefore apply as the proposal is to only amend the steviol glycoside specifications into 4 distinct and separate specifications including 1) plant extracts, 2) fermentation products 3) bioconversion products, and 4) glucosylated products. For a complete listing of all food products, food categories and use levels, please see the GSFA for steviol glycosides.

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))

In the United States (U.S.), a high purity rebaudioside D or M material manufactured by Cargill Inc. using a GM *Saccharomyces cerevisiae* is considered Generally Recognized as Safe (GRAS) and has been U.S. Food and Drug Administration (FDA) notified (GRN 626) The fermentation technology is similar to DSM's rebaudioside A material produced using a GM *Yarrowia lipolytica* (GRN 632) that JECFA evaluated in 2016 and which resulted in the issuance of a new JECFA specification.

Blue California's rebaudioside D material produced using bioconversion technology using an isolated enzyme produced from GM *Pichia pastoris* is likewise GRAS and has been U.S. FDA notified (GRN 715) and received a "no questions' response.. Again, this rebaudioside D material is manufactured in a similar manner to Blue California's rebaudioside M that is likewise generated from enzymes isolated from GM *Pichia pastoris.* Blue California's rebaudioside M product has been U.S. FDA notified (GRN 667) and received a 'no questions'

response, and is currently on the list of priority substances proposed for evaluation by JECFA.

Enzyme modified or glycosylated steviol glycosides are an approved food additive in Japan and have a safe history of use for over 25 years. Enzymatically modified stevia is also listed in the Korea Food Additives code and is regulated in Malaysia as a sweetening substance. Furthermore, 7 GRAS notices (GRN 337, 375, 448, 452, 607, 656 and 662) using various manufacturing processes have been submitted through the U.S. FDA notification procedure and received a "no questions' response.

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

Toxicological data

The toxicology data to support the safety of steviol glycosides that are produced through fermentation or bioconversion processes or which undergo enzymatic glycosylation, are available and can be provided upon request. Overall, the data supporting the safety of steviol glycosides that meet the current JECFA specification or are enzymatically modified incorporating additional glucose moieties, are corroborated through a similar metabolism profile for all steviol glycosides and an in depth toxicological safety data package. As such, these data support the fact that the steviol glycosides produced through the new technologies are covered by the current steviol glycoside ADI. The safety of these materials have previously been endorsed by the JECFA and other international agencies.

(i) Metabolic and pharmacokinetic studies

Available

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

All available

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

Clinical data available including studies in diabetics

(iv) Other data

History of safe use

Technological Data

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

Specifications for the identity and purity of those SG products that meet the fermentation, bioconversion and enzyme modified (glucosylated) production criteria are available

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

The additive steviol glycosides is of principle interest for its sweetening properties. Steviol glycosides (including those that undergo additional glucosylation) are known to have a solubility ranging between "freely to slightly soluble in water". The sweetening power of the various individual and combinations of the various steviol glycosides ranges between 200 and 350 x sweeter than sucrose. The individual glycosides and combination products are thermally and hydrothermally stable for use in many different foods, including acidic beverages under normal conditions of processing and storage.

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 levels of steviol glycosides produced using the fermentation, bioconversion and enzyme modified procedures will be identical to those currently accepted for steviol glycosides extracted from the stevia plant. These will be used in a range of foods and beverages based upon technological function.

Since the proposed changes will be related to the specifications only, there are no proposed changes to the food categories/use levels listed in the GSFA.

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

Since no changes in the categories or use levels for steviol glycosides are being requested the JECFA dietary intake assessment outcome in 2016 is still considered appropriate.

Other information (as necessary/identified)

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

December 2018