

# CODEX ALIMENTARIUS COMMISSION



Food and Agriculture  
Organization of the  
United Nations



World Health  
Organization

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Agenda Item 7

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## JOINT FAO/WHO FOOD STANDARDS PROGRAMME

### CODEX COMMITTEE ON FOOD ADDITIVES

#### Fifty-Fourth Session

#### PROPOSALS FOR ADDITIONS AND CHANGES TO THE PRIORITY LIST OF SUBSTANCES PROPOSED FOR EVALUATION BY JECFA (replies to CL 2023/47-FA)

(Comments of China, Japan, Kenya, Peru, the United States Pharmacopeial Convention (USP))

#### China

|   |  |
|---|--|
| <b>Name of Substance(s):</b>  | Transglutaminase (EC 2.3.2.13)   |
| <b>Question(s) to be answered by JECFA</b><br><i>(Provide a brief justification of the request in case of re-evaluations)</i> | To evaluate the safety of transglutaminase derived from <i>Streptomyces mobaraensis</i> strain M2020197 when used as processing aid and establishment of specifications. |

1. Proposal for inclusion submitted by:

Dongsheng Biotech (Taixing) Co., Ltd.

2. Name of substance; trade name(s); chemical name(s), IUPAC name, C.A.S number (as applicable):

Transglutaminase

Chemical name: protein-glutamine:amine  $\gamma$ -glutamyltransferase

Synonyms: Factor XIIIa; fibrinolyase; fibrin stabilizing factor; glutamylpeptide  $\gamma$ -glutamyltransferase; polyamine transglutaminase; tissue transglutaminase; R glutamyl-peptide:amine  $\gamma$ -glutamyl transferase

Trade name: "Prolink™", "Acelink" and "TG" ranges of transglutaminase-based enzymatic preparations

CAS number: 80146-85-6

3. Names and addresses of basic producers:

Dongsheng Biotech (Taixing) Co., Ltd.

Room 801, Building 3, Lane 2301 Yishan Road

Minhang District,

Shanghai, China

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

Marco Marcucci

R&D Director

Dongsheng Biotech (Taixing) Co., Ltd.

No. 91-92 Junmin Road,

Huangqiao, Taixing, Taizhou, Jiangsu

China

The manufacturer is represented by:

Shahrzad Tafazoli, Ph.D.

Intertek Health Sciences Inc.

2233 Argentia Road, Suite 201

Mississauga, Ontario Canada

L5N 2X7

5. Justification for use:

The request relates to the evaluation of transglutaminase from non-genetically modified *Streptomyces mobaraensis* strain M2020197 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and is justified based on the commercial availability of the enzyme preparation in various global markets.

Transglutaminase from non-genetically modified *S. mobaraensis* strain M2020197 is intended for use during food and beverage processing to catalyse the formation of cross-linking of bonds between glutamine and lysine residues within and between proteins in food. These cross-linkages increase the size and structure of food proteins, thus modifying the physical properties of the food such as breaking strength, texture, and moisture retention. These modified physical properties ultimately impact the sensory attributes of the food.

6. 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 transglutaminase from *Streptomyces mobaraensis* strain M2020197 is intended to be used are outlined in the table below.

| The Codex GSFA Food Category   | GSFA Food Category No. | Representative Food Uses <sup>a</sup>  | Max. Level of Transglutaminase (mg TOS/kg food) |
|--|------------------------|--|---|
| Fermented milks (plain)  | 01.2.1                 | Yoghurt  | 4.34  |
| Cheese and analogues   | 01.6                   | Natural cheese, processed cheese, cream cheese   | 97.56   |
| Dairy-based desserts (e.g. pudding, fruit or flavoured yoghurt)                                      | 01.7                   | Frozen dairy desserts  | 17.34   |
| Breakfast cereals, including rolled oats   | 06.3                   | Ready-to-eat cereals   | 43.35   |
| Pastas and noodles and like products (e.g., rice paper, rice vermicelli, soybean pastas and noodles) | 06.4                   | Pasta and noodles  | 17.34   |
| Soybean curd (tofu)  | 06.8.3                 | Tofu and soybean products  | 19.87   |
| Semi-dehydrated soybean curd   | 06.8.4                 | Tofu and soybean products  | 19.87   |
| Dehydrated soybean curd (kori tofu)  | 06.8.5                 | Tofu and soybean products  | 19.87   |
| Fermented soybean curd   | 06.8.7                 | Soya yoghurt   | 8.67  |
| Bread and ordinary bakery wares  | 07.1                   | Bread, pizza, croissant, brioche, rolls, cakes, pies, doughnuts, and similar foods   | 17.34   |
| Fine bakery wares (sweet, salty, savoury) and mixes  | 07.2                   |  | 17.34   |
| Processed meat, poultry, and game products in whole pieces or cuts                                   | 08.2                   | Fresh/cooked/smoked/dry-fermented sausages, cooked hams, meat balls, burgers, liver pate, Beef steak, pork steak, bacon, chicken medallions, turkey medallions | 65.04   |
| Processed comminuted meat, poultry, and game products  | 08.3                   |  | 65.04   |
| Frozen fish, fish fillets, and fish products, including  | 09.2.1                 |  | 65.04   |

|   |                               |  |  |
|---|-------------------------------|--|--|
| mollusks, crustaceans, and echinoderms  |                               | Fish burgers, scallops, shrimps, surimi, salmon medallions, and other structured / textured fish meat products or fish paste |  |
| Frozen battered fish, fish fillets, and fish products, including mollusks, crustaceans, and echinoderms | 09.2.2                        |  | 65.04  |
| Frozen minced and creamed fish products, including mollusks, crustaceans, and echinoderms               | 09.2.3                        |  | 65.04  |
| Cooked fish and fish products   | 09.2.4.1                      |  | 65.04  |
| Fried fish and fish products, including mollusks, crustaceans, and echinoderms                          | 09.2.4.3                      |  | 65.04  |
| Protein products other than from soybeans   | 12.10                         | Meat imitates, imitation yoghurt (other than soy)  | 8.67   |
| Prepared foods  | 16.0                          | Pizza, burritos, tacos, tortillas, and similar grain-based mixed dishes  | 17.34  |
| <b>The Codex GSFA Food Category</b>   | <b>GSFA Food Category No.</b> | <b>Representative Food Uses<sup>a</sup></b>  | <b>Max. Level of Transglutaminase (mg TOS/kg food)</b> |
|   |                               | Meat-based mixed dishes  | 65.04  |

7. 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 general, microbial transglutaminase from non-genetically modified *Streptomyces mobaraensis*, without reference or restriction to any specific production strain, is legally traded and authorized for use in China, Japan, Taiwan, South Korea, Australia and New Zealand, Philippines, Indonesia, Malaysia, Singapore, Thailand, India, Egypt, Israel, South Africa, Mexico, Brazil, Chile, Uruguay, and Argentina. The transglutaminase obtained by *Streptomyces mobaraensis* strain M2020197 has received “no questions” from the U.S. FDA regarding the generally recognized as safe (GRAS) status of the enzyme for use in food (GRN 1021), and has been approved for use as a food additive by Health Canada and as a food enzyme in Denmark and France.

8. Are you aware of any current impediments in international trade due to lack of a JECFA evaluation and/or Codex standard? If so, please provide details.

No.

9. Are you aware of risk assessments, either on-going or completed within the last 10 years, at a national or regional level for this additive? If so, please provide the name, address and contact details of the organization having performed the risk assessment.

The transglutaminase from *Streptomyces mobaraensis* strain M2020197, as manufactured by Dongsheng Biotech (Taixing) Co., Ltd., has Generally Recognized as Safe (GRAS) status in the U.S. under GRN 1021, which received a letter of “no questions” from the U.S. FDA, and a risk assessment of the enzyme have been performed by Health Canada and Danish Veterinary and Food Administration (DVFA). As a result, transglutaminase from *Streptomyces mobaraensis* strain M2020197 has been authorised for use in Canada, Denmark, and France by mutual recognition to Denmark. An application for authorisation of the enzyme within the European Union (EU) has been submitted in 2021, and a risk assessment is currently ongoing by the European Food Safety Authority (EFSA). The application reference number is EFSA-Q-2021-00651.

10. Please provide details if this food additive is of particular relevance to the livelihood and food safety in developing countries

The enzyme is intended for use in food processing to create protein cross-linking bonds that result in an increase in size and structure of food proteins, thus improving the physical and chemical properties of the food, such as

its breaking strength, texture, and moisture retention, and ultimately improving the sensory attributes of the food. For example, one of the most commonly known uses of transglutaminase is to “reform” meats to join small pieces of meat into larger pieces (e.g., in the production of sausages or surimi). When added to bakery products (e.g., within the dough), transglutaminase improves the rheological characteristics of dough and the physicochemical quality of the final product by polymerizing proteins (i.e., gliadin and high molecular weight glutenins in wheat), thus forming intermolecular crosslinks and strengthening the protein structure and elasticity, as well as the water-holding capacity and thermal stability of the final product. The use in bakery products ultimately improves the cooking quality and reduced loss of the food product during cooking. The described food uses of transglutaminase have advantageous benefits of reducing food waste during food processing. Approximately 13% of the world’s food is lost through the supply chain from post-harvest up to retail<sup>1</sup>. The FAO recognizes that reduction of food loss and food waste “can play a key role in the transformation of agrifood systems by increasing the availability of food, contributing to food security, healthy diets, and building resilience”, as well as aiding in the reduction of greenhouse gas emissions. Considering the global need for a sustainable food supply, transglutaminase is particularly relevant to improve the livelihood of the global population.

11. Please indicate the type of data that are available in the table below.

Ensure that the available data are directly relevant to the substance of interest in this request. In particular, for substances obtained from natural resources, characterization of the products in commerce and a relevant set of biochemical and toxicological data on such products are essential for JECFA to develop a specifications monograph and the related safety. Such data/information typically include: components of interest; all components of the final products; detailed manufacturing process; possible carryover of substances; etc.

|  | <b>Data available?<br/>(Y/N)</b>  |
|--|---|
| <b>Toxicological data</b>  |   |
| (i) Metabolic and pharmacokinetic studies (please specify)   | N   |
| (ii) Short-term toxicity, long-term toxicity/carcinogenicity, reproductive toxicity, and developmental toxicity studies in animals and genotoxicity studies (please specify) | Y<br><i>Short-term toxicity: 90-day repeated-dose oral toxicity study in rodents (OECD Test Guideline 408)</i><br><i>Genotoxicity: bacterial reverse mutation test (OECD Test Guideline 474) and in vitro micronucleus test (OECD Test Guideline 487)</i> |
| (iii) Epidemiological and/or clinical studies and special considerations (please specify)  | Y   |
| (iv) Other data (please specify)   | Y<br><i>Bioinformatics of the enzyme (allergenicity, toxigenicity) and production organism (pathogenicity, antimicrobial resistance)</i>  |
| <b>Technological data</b>  |   |

<sup>1</sup> <https://www.fao.org/3/cc1403en/online/cc1403en.html#12>

|   |  |
|---|--|
| (i) Specifications for the identity and purity of the listed substances (specifications applied during development and toxicological studies; proposed specifications for commerce) | Y  |
| (ii) Technological and nutritional considerations relating to the manufacture and use of the listed substance   | Y  |
| <b>Dietary exposure assessment data</b>   |  |
| (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                        | Y  |
| (ii) Estimation of dietary exposures based on food consumption data for foods in which the substance may be used.   | Y  |
| <b>Other information:</b> (please specify)  | Y<br><i>Absence of viable cell of the production strain in the final product</i> |

12. Specify earliest date when data can be made available to JECFA. (Data shall only be submitted in response to a JECFA call for data; **do NOT include any data intended for JECFA to this form.**)

As soon as requested.

### Japan

In addition to the two proposals mentioned in CX/FA 24/54/10, Japan would like to make proposals regarding No. 18 and No. 21 in CL 2023/47-FA Annex 3 Part B.<sup>2</sup>

First, regarding No. 18 Phosphodiesterase from *Penicillium citrinum*, “Phosphodiesterase” was renamed to Ribonuclease P in JECFA 92.<sup>3</sup>

Furthermore, in JECFA92, toxicological evaluations and exposure assessments have been completed for Ribonuclease P enzyme preparation from *P. citrinum* AE-RP.<sup>4</sup>

Therefore, Japan proposes to remove No. 18 Phosphodiesterase from *Penicillium citrinum* from the list.

CL 2023/47-FA Annex 3 Part B ( p.17,18 )<sup>1</sup>

PART B: LIST OF SUBSTANCES USED AS PROCESSING AIDS PROPOSED FOR EVALUATION BY JECFA

| No | Substance(s)  | General information   | Comments about the request   |
|----|---|---|--|
| 18 | Phosphodiesterase from<br><i>Penicillium-citrinum</i> | <b>Type of request:</b> Safety assessment and Establishment of specifications<br><b>Proposed by:</b> Japan<br><b>Year requested:</b> 2017 (CCFA49)<br><b>Data availability:</b> December 2018<br><b>Data provider:</b><br>Amano Enzyme Inc. | <b>Basis for request:</b><br>The enzyme is used in processing yeast products by hydrolysing RNA, thereby increasing ribonucleotide levels and improving umami flavour.<br><br>Possible issues for trade: currently unidentified. |

<sup>2</sup> [fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202023-47%252Fcl23\\_47e.pdf](https://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202023-47%252Fcl23_47e.pdf)

<sup>3</sup> [9789240054646-eng.pdf \(who.int\)](https://www.who.int/publications/m/item/9789240054646-eng) p.2

<sup>4</sup> [9789240054646-eng.pdf \(who.int\)](https://www.who.int/publications/m/item/9789240054646-eng) p.37-42

|  |  |  |
|--|--|--|
|  | Mr. Tomonari Ogawa<br>( <a href="mailto:tomonari_ogawa@amano-enzyme.com">tomonari_ogawa@amano-enzyme.com</a> ) |  |
|--|--|--|

Second, regarding No. 21 Ribonuclease from *Penicillium citrinum* RP-4, there is a sponsor in Japan who would like to become a data provider.

According to the sponsor, it's expected data would be available in March 2025.

CL 2023/47-FA Annex 3 Part B ( p.24 ) <sup>1</sup>

PART B: LIST OF SUBSTANCES USED AS PROCESSING AIDS PROPOSED FOR EVALUATION BY JECFA

| No | Substance(s)                                       | General information  | Comments about the request   |
|----|--|--|--|
| 21 | Ribonuclease from <i>Penicillium citrinum</i> RP-4 | <p><b>Type of request:</b> Data pending to complete evaluation – Evaluation by JECFA92</p> <p><b>Proposed by:</b> JECFA</p> <p><b>Year requested:</b> 2023 (CCFA53)</p> <p><b>Data availability:</b> <del>To be confirmed at CCFA54</del> March 2025</p> <p><b>Data provider:</b> <del>To be confirmed at CCFA54</del></p> <p>Amano Enzyme Inc.<br/>Mr. Hiromichi Yoshida (<a href="mailto:hiromichi_yoshida@amano-enzyme.com">hiromichi_yoshida@amano-enzyme.com</a>)</p> | <p><b>Basis for request:</b> During its recent evaluation of Ribonuclease P, the 92nd JECFA noted that ribonuclease P can also be produced by <i>P. citrinum</i> RP-4, but insufficient information was available on the enzyme concentrate produced from this strain.</p> <p>To evaluate the safety of ribonuclease P from <i>P. citrinum</i> RP-4, toxicological studies with well-characterized enzyme concentrate are required.</p> <p><b>Possible issues for trade:</b> currently unidentified.</p> |

### Kenya

**Position:** Kenya supports the priority lists and ranking based on consumer health risks, international trade concerns, and data availability.

**Rationale:** The ranking should prioritize food additives that are of major concern in relation to consumer's safety and health, facilitate fair trade, and where data has been provided.

### Peru

The Codex Secretariat by Circular Letter CL 2023/47-FA requests information and comments on the list of priority substances proposed for evaluation by JECFA, and invites you to: (i) submit your comments on substances already included in the list of priority substances proposed for evaluation by JECFA; (ii) submit information on new substances for inclusion in the priority list, and/or (iii) confirm previous requests and availability of data, in this regard Peru specifies that: **(i)** It has no comments on substances already included in the priority list of substances proposed for evaluation by JECFA, **(ii)** We do not submit information on new substances for inclusion in the priority list, and **(iii)** We do not make prior requests or submit data. We also point out that Peru agrees with the list of priorities of substances proposed for evaluation by JECFA.

La Secretaría del Codex mediante Carta Circular CL 2023/47-FA solicita información y observaciones sobre la lista de prioridades de sustancias propuestas para su evaluación por el JECFA, e invita a: : i) enviar sus observaciones sobre sustancias ya incluidas en la lista de prioridades de sustancias propuestas para su evaluación por el JECFA; ii) presentar información sobre nuevas sustancias para su inclusión en la lista de prioridades, y/o iii) confirmar las anteriores solicitudes y disponibilidad de datos, al respecto Perú precisa que: **i)** No tiene observaciones sobre las sustancias ya incluidas en la lista de prioridades de sustancias propuestas para su evaluación por el JECFA, **ii)** No presentamos información sobre nuevas sustancias para inclusión a la lista de

prioridades, y **iii**) No realizamos anteriores solicitudes, ni presentamos datos. Asimismo, precisamos que Perú está de acuerdo con la lista de prioridades de sustancias propuestas para su evaluación por el JECFA.

#### **The United States Pharmacopeial Convention (USP)**

USP understands that the inclusion of Bentonite (INS 558) on the PRIORITY LIST OF SUBSTANCES PROPOSED FOR EVALUATION BY JECFA (Appendix XI of REP23/FA) includes a recommendation from CCCF14 that JECFA "...review the lead specifications for diatomaceous earth and activated carbon and... evaluate available data to support development of a lead specification for bentonite." Further, according to item 134 in REP23/FA, we understand that CCFA53 "...emphasized that should confirmation of data availability not be provided at CCFA54 a reply to CCCF would be put forward, noting the lack of a data sponsor, and that CCFA may not be able to respond to CCCF's request."

USP would like to confirm to CCFA that we are prepared to supply JECFA with data on lead levels present in commercially available bentonite, diatomaceous earth, and activated carbon products, including products manufactured and marketed for use in foods. Data has been gathered by one of USP's laboratories from multiple samples and multiple manufacturers. In all cases, samples were tested in duplicate using inductively coupled plasma – optical emission spectrometry (ICP-OES) technology.