CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 6 **CX/FA 17/49/12 Add.1**
March 2017

JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON FOOD ADDITIVES

Forty-Ninth Session

Macao SAR, China, 20-24 March 2017

PROPOSED DRAFT REVISION TO THE INTERNATIONAL NUMBERING SYSTEM (INS) FOR FOOD ADDITIVES (CAC/GL 36-1989)

(Comments at Step 3)

Comments of Brazil, Chile, Ecuador, European Union, Japan, Singapore, United States of America, AMFEP, ETA, EU Speciality Food Ingredients, IACM, IFAC and NATCOL

Brazil

Table 1: New or additional technological purpose

No comments.

Table 2: Deletion of additive purpose

Enzymes deletion

Brazil would like to point out some concerns about this issue, since some countries consider some enzymes as food additives in some cases, because these substances will be present in the final product. There are some examples as the use of proteases in wheat flour treatment or the use of enzymes in seasonings. These cases fall into the food additives definition of the GSFA. These products are sold direct to final clients and then you have to label these substances as food additives, once they will be present activated in the final product. For these reason, Brazil believes further discussion is needed in order to clearly clarify the use of enzymes by food industry and possible impacts of this approach.

Deletion of nisin (INS 234) and pimaricin (INS 235)

Brazil, does not support deletion of these food additives, once Anti-microbial resistance was evaluated by JECFA, when JECFA evaluated these substances. If there are new evidences that opposes JECFA's outcome it should be submitted again for reevaluation, before take any action on this issue, since these food additives are listed to several Food Categories and the consequential deletion of these provisions may have a big economic impact.

Furthermore, Nisin was recently reevaluated by JECFA in 2013 and anti-microbial resistance development was not associated to this food additive.

Chile

Information: In the table 1 for Sucralose INS 955, is propose agree the clase functional of flovour enhancer.

Chile comments: Sucralose is a sweetener, so that Chile wants to know the reasons for the inclusion of the technological function accentuador of the flavor, since the definition of this functional class is "substance that helps to enhance the flavor" is not the substance that sweetens.

Information: Table 1 proposes to include the functional classes, humectant, stabilizer and texturizing agent for Trehalosa.

Chile comments: Trehalose, is used as an ingredient, the functions presented (humectant, stabilizer and texturizing agent) are secondary and therefore should be considered as an ingredient unless there are studies in this regard.

Information: In Table 2 it is proposed to remove Nisin (INS 234) and Natamycin (INS 235) from the list of additives arguing that they are antibiotics and antibiotics cannot be used as food additives.

Chile comments:

According to the latest definition of the World Health Organization (WHO) 2011, the term antibiotic is used as a synonym for antibacterial substances used to treat bacterial infections in humans and animals. Natamycin is not an antibiotic according to WHO (http://www.natamycin.com/en/regulatory).

Natamycin is a food preservative that is approved and used in more than 150 countries around the world. It is importan to note that world-renowned experts (JECFA, EFSA, FDA) have evaluated their safety, which are classified as safe for consumption, these assessments still remain valid.

Natamycin has been used for more than 30 years to prolong the storage life of various foods with the elimination of yeasts and molds, and the inhibition of mycotoxin proliferation. It is associated with the treatment of cheeses surfaces, as natural inhibitor of fungi has no effect on bacteria and therefore has nothing in common with regular medicinal antibiotics that are prescribed to treat bacterial infections.

JECFA evaluated the toxicology of natamycin in 1976 and recommended an acceptable daily intake of 0-0.3 mg / kg body weight. The Committee agreed that the data demonstrated that natamycin would not present problems related to the development of clinically significant microbial resistance or cross-resistance.

On the other hand, Nisin is a bacteriocin that is used as a food preservative; Is recognized by the FDA with the GRAS (Generally Recognized as safe) category. It is produced naturally in some dairy products and is used in food production and as an additive in dairy products to prevent decomposition caused by Gram-positive bacteria, especially the Clostridium, Staphylococcus, Bacillus and Lysteria genera (Ma del Carmen Monroy, *et al*., 2009).

Bacteriocides produced by lactic bacteria are considered to be health-safe microorganisms, have been consumed in fermented foods for innumerable generations without adverse effects on the population (Drugs *et al*., 2003). , 2006; Millete *et al*., 2008)

Due to its protean nature, bacteriocins are inactivated by proteases, including those of pancreatic and gastric origin, because they are inactivated during their passage through the gastrointestinal tract, without being absorbed as active compounds, thus being harmless to the consumer (SC Beristain -Bauza *et al*, 2012, Quintero, 2006).

Therefore, if well we support overall action plan on antibiotic resistance by WHO, it should been consider, for the reasons explained above that both Nisin and Natamycin are not considered to be antibiotics by the same organism and therefore do not should be removed from the list of additives, its immediate suspension as additives would have an immediate impact on many cheese producers worldwide, which would constitute a trade barrier.

Ecuador

Ecuador is grateful to the electronic working group (EWG) led by Iran for the work carried out in this document.

Concerning Table 2 of Annex 1, we wish to state that Ecuador supports the removal of the following additives:

INS	Food Additive	Functional Class	Technological Purpose
~~1100~~	~~Amylases~~		
~~1100 (i)~~	~~alpha Amylase from *Aspergillus oryzae* var.~~	~~Flour treatment agent~~	~~flour treatment agent~~
~~1100 (ii)~~	~~alpha Amylase from *Bacillus stearothermophilus*~~	~~Flour treatment agent~~	~~flour treatment agent~~
~~1100 (iii)~~	~~alpha Amylase from *Bacillus subtilis*~~	~~Flour treatment agent~~	~~flour treatment agent~~
~~1100 (iv)~~	~~alpha-Amylase from *Bacillus megaterium* expressed in *Bacillus subtilis*~~	~~Flour treatment agent~~	~~flour treatment agent~~
~~1100 (v)~~	~~alpha Amylase from *Bacillus stearothermophilus* expressed in *Bacillus subtilis*~~	~~Flour treatment agent~~	~~flour treatment agent~~
~~1100 (vi)~~	~~Carbohydrase of *Bacillus licheniformis*~~	~~Flour treatment agent~~	~~flour treatment agent~~

~~1101~~	~~Proteases~~		
~~1101 (i)~~	~~Protease from *Aspergillus oryzae* var.~~	~~Flour treatment agent~~ ~~Flavour enhancer~~ ~~Stabilizer~~	~~flour treatment agent~~ ~~flavour enhancer~~ ~~stabilizer~~

Rationale:
Given that enzymes act as processing aids, we thus support that they should not be in the list of additives to be declared since most of them act during processing and afterwards they are inactivated, and are not present in the final products for human consumption.

European Union

The European Union and its Member States (EUMS) would like to thank Iran for chairing the electronic Working Group and developing the discussion paper.

The EUMS would like to provide the following comments on the proposed draft changes and/or additions to the INS as outlined in Annex 1 to CX/FA 17/49/12:

Table 1, Trehalose

The EUMS do not support listing of trehalose in CAC/GL 36-1989.

The EUMS consider that trehalose, a naturally occurring disaccharide, is a food ingredient that does not fall under the Codex definition of a food additive.

Table 2

The EUMS do not support the proposed deletion of substances listed in Table 2 of CX/FA 17/49/12.

The use of those substances is currently recognised in the GSFA therefore the EUMS do not consider appropriate to delete them from the INS list.

If some Members or interested International Organisations are of the view that there are safety concerns as regards certain substances listed in the GSFA or that such substances cannot be classified as food additives, the CCFA has another appropriate tools how to address such issues (i.e. requesting JECFA to re-assess the safety in the former case or requesting a revision of the adopted food additive provisions in the GSFA in the latter).

Japan

Japan appreciates Iran for chairing the electronic working group on INS, and welcomes the opportunity to provide our comments.

1. Elderberry color

Japan would like to propose that “INS 163(iv)” be editorially changed to “INS 163(ix)” for Elderberry color in the Annex 1 of CX/FA17/49/12 document. INS 163(iv) is already assigned to Purple corn colour in the *Class Names and the International Numbering System for Food Additives* (CAC/GL 36-1989).

2. Sodium polyacrylate

Japan is of the opinion that “INS 1210” would be a suitable candidate for Sodium polyacrylate, since similar polymers such as methacrylates have INS 1200’s and CAC/GL 36-1989 shows that INS after 1209 is vacant.

Singapore

Singapore notes from the document CX/FA 17/49/12 that the electronic working group on the International Numbering System (INS) for food additives has proposed the deletion of the following food additives from the document CAC/GL 36-1989:

(a) amylases (INS 1100 i, ii, iii, iv, v, vi), proteases (INS 1101 i, ii, iii, iv, v, vi) and lipases (INS 1104) as these are digestive enzymes which have been broadly used in therapy of digestive tract diseases. Therefore there could be an imbalance in the digestive process if these digestive enzymes are systematically used in food.

(b) nisin (INS 234) and pimaricin/natamycin (INS 235) because these are antibiotics and should not be used as food additives. The eWG believes that excluding these two additives from the INS list is one of a few decisions which could help solve the problem of anti-microbial resistance (AMR).

Singapore objects to the proposed deletions due to the following reasons:

Reason #1

The Codex document "Class Names and International Numbering System for Food Additives" (CAC/GL 36-1989) clearly states that the "*International Numbering System for Food Additives (INS) is intended as a harmonised naming system for food additives. Inclusion in the INS does not imply approval by Codex for use as food additives. The list may include those additives that have not been evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).*" The document further states that the primary purpose of this document is to serve as a means of identification for food additives.

As such, concerns over the physiological effects and/or potential to lead to antimicrobial resistance should not affect its INS number and/or its listing in this document. As a case in point, INS 216 (propyl para-hydroxybenzoate) remains listed in CAC/GL 36-1989 despite the removal of additive specifications by JECFA in 2006 and the subsequent discontinuation of draft provisions in the GSFA due to concerns over its safety.

Instead, it is the "General Standard for Food Additives" (GSFA) [CODEX STAN 192-1995] that is "the single authoritative reference point for food additives" in Codex and "sets forth the conditions under which food additives may be used in all foods". Food categories or individual food items in which the use of food additives is not acceptable, or where use should be restricted, are specified in the GSFA. All of the additives proposed for deletion by the eWG are currently listed in the GSFA (refer to Annex I).

Food additives that are listed in the GSFA have gone through safety assessments by JECFA before they are considered for inclusion in the GSFA. Moreover, in the case of the enzymes (amylases, proteases and lipases), these would have been denatured and they are no longer active in the final food product, going by their use as processing aids in the manufacture of food or food ingredients. In any case, should the eWG have any concerns over the safety of the food additives that it has proposed for deletion, it should request a re-evaluation of these additives by JECFA.

Reason #2

Singapore notes that the eWG has proposed the deletion of nisin and natamycin in the belief that this could help solve the problem of anti-microbial resistance (AMR).

We believe that the issue of nisin and AMR has been dealt with in the 48th Session of the Codex Committee on Food Additives (CCFA). We would like to make reference to the following comments submitted by IFAC with regard to AMR, documented in CRD 16 (page 3 and 8):

a) Nisin A is a food preservative. It is not approved for clinical therapeutic use in humans

b) Bacterial nisin resistance has generally not been associated with cross-resistance against antibiotics used clinically for treatment of infectious disease

c) Despite widespread use of nisin as a food preservative for more than fifty years, reports of acquisition of resistance in susceptible bacteria have generally been restricted to laboratory studies of pure bacterial cultures under artificial selection conditions rather than "in the field" i.e. in bacteria contaminating foods or colonizing animals as normal microbiota.

d) Use of nisin as a food preservative is not likely to have any clinical impact on bacterial pathogens causing human infections.

e) There does not appear to be significant issues with natural development or transmission of antimicrobial resistance arising from nisin use.

With regard to natamycin, we note that the European Food Safety Authority (EFSA)[1] was asked to provide a scientific opinion on the safety of natamycin (E 235) for use as a food additive, and on the issue of antimicrobial resistance to natamycin. EFSA concluded that there was no concern for the induction of antimicrobial resistance from the use of natamycin as a food additive.

Based on the available information, we are of the view that there is insufficient scientific evidence that use of nisin and natamycin would lead to antimicrobial resistance.

Reference:

1. EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS); Scientific Opinion on the use of natamycin (E 235) as a food additive. EFSA Journal 2009;7(12):1412 [25 pp.]. doi:10.2903/j.efsa.2009.1412.

Annex 1

GENERAL STANDARD FOR FOOD ADDITIVES (CODEX STAN 192-1995)

INS number	Name of Food Additive	Function Class
234	Nisin	Preservative
235	Natamycin (pimaricin)	Preservative
1100(i)	alpha-Amylase from Aspergillus oryzae var.	Flour treatment agent
1100(ii)	alpha-Amylase from Bacillus stearothermophilus	Flour treatment agent
1100(iii)	alpha-Amylase from Bacillus subtilis	Flour treatment agent
1100(iv)	alpha-Amylase from Bacillus megaterium expressed in Bacillus subtilis	Flour treatment agent
1100(v)	alpha-Amylase from Bacillus stearothermophilus expressed in Bacillus subtilis	Flour treatment agent
1101(i)	Protease from Aspergillus orizae var.	Flavour enhancer, Flour treatment agent, Stabilizer
1104	lipases	Flavour enhancer

Natamycin (INS 235) has been evaluated and established at the 20th JECFA with an ADI 0.3 mg/kg bw, for use as a fungicidal preservation.

http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-293.pdf

Nisin (INS 234) has been evaluated and established at the 77th JECFA with an ADI 2 mg/kg bw, for use as an antimicrobial preservative.

http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph14/additive-295-m14.pdf

United States of America

This responds to CX/FA 17/49/12 (December 2016): **Proposed Draft Revision to the International Numbering System (INS) for Food Additives (CAC/GL 36-1989).** The United States wishes to thank Iran for their role in chairing the electronic working group (eWG) for the International Numbering System (INS). The United States appreciates the opportunity to provide the following comments for consideration at the forthcoming 49th Session of the Codex Committee on Food Additives (CCFA).

Comments on "Table 2: Deletion of Additive Purpose"

Nisin (INS 234) and Natamycin (Pimaricin) (INS 235)

The United States strongly opposes the proposal made in CX/FA 17/49/12 to remove Nisin (INS 234) and Natamycin (Pimaricin) (INS 235) from the INS. Removing the listings for Nisin and Natamycin (Pimaricin) from the INS would require the revocation of all adopted provisions and discontinuation of all provisions in the step process for these additives in the General Standard for Food Additives (GSFA). Both Nisin and Natamycin (Pimaricin) have been evaluated for their safe use in food by the Joint FAO/WHO Expert Committee on Food Additives (JECFA). Nisin was reviewed most recently at the 77th JECFA (2013) at which an acceptable daily intake (ADI) of 0-2 mg/kg bw was established.[1] Natamycin (Pimaricin) was most recently evaluated at the 57th JECFA (2002) at which an ADI of 0.3 mg/kg bw was reestablished.[2] In addition, Nisin is affirmed as Generally Recognized as Safe (GRAS) in the United States for use in certain foods as an antimicrobial agent under 21 CFR 184.1538, and Natamycin (Pimaricin) is permitted for use in certain foods in the United States as an antimycotic agent under 21 CFR 172.155.

One of the reasons provided in CX/FA 17/49/12 for removing Nisin and Natamycin (Pimaricin) from the INS is anti-microbial resistance (AMR) resulting from the use of Nisin and Natamycin (Pimaricin) in the food supply. The potential for AMR was addressed by JECFA in the toxicological monographs published by the 77th JECFA for Nisin,[3] and the 57th JECFA for Natamycin (Pimaricin).[4] No AMR concerns were raised by JECFA from the use of Nisin or Natamycin (Pimaricin) as preservatives in food.

We would also note that the CCFA recommended and the Codex Alimentarius Commission adopted four provisions for Nisin at the 39th Session of the Commission in 2016.

[1] Evaluation of certain food additives and contaminants (Seventy-fourth report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 983, 2013.
[2] Evaluation of certain food additives and contaminants (Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives) WHO Technical Report Series, No. 909, 2002.
[3] Safety evaluation of certain food additives and contaminants, WHO Food Additives Series, No. 68, 2013.
[4] Safety evaluation of certain food additives and contaminants, WHO Food Additives Series, No. 48, 2001.

In conclusion, the United States believes that Nisin (INS 234) and Natamycin (Pimaricin) (INS 235) are safe and suitable for their intended use in food, and should not be removed from the INS.

Amylases (INS 1100(i), (ii), (iii), (iv), (v), (vi)), Proteases (INS 1101(i), (ii), (iii), (iv), (v), (vi)), and Lipases (INS 1104)

A proposal was made to the INS electronic working group (eWG) to remove certain enzymes from the INS (Amylases (INS 1100(i), (ii), (iii), (iv), (v), (vi)), Proteases (INS 1101(i), (ii), (iii), (iv), (v), (vi)), and Lipases (INS 1104)) based on the argument that these enzymes are not used as food additives, but as processing aids. If indeed these enzymes only function as processing aids, and not as food additives, the United States does not have a concern regarding their removal from the INS.

However, the United States notes that CX/FA 17/49/12 contains language which implies that the enzymes should be removed from the INS due to safety concerns from their use in food. We are of the view that this language does not reflect the discussions held by the eWG on the INS. We are not aware of any safety concerns from the use of these enzymes in food. In fact, all of the amylases, lipases, and proteases that are currently included in the GSFA have been assigned ADIs of "not specified" by JECFA, meaning that on the basis of available data, they have very low toxicity and do not represent a hazard to health from their use in food.

Association of Manufacturers and Formulators of Enzyme Products (AMFEP)

AMFEP calls for crucial amendments to the Proposed draft revision to the International Numbering System (INS) for food additives (CAC/GL 36-1989)[5], as put forward by the Iran chair of the INS WG for discussion at CCFA (Agenda item 6) due to in brief, the following reasons;

- The document was amended with arguments that were not discussed in the eWG
- The arguments are not relevant for the decision to delete enzymes in the INS list (since they are not food additives)
- The arguments unrightfully question the safety of enzymes used as processing aids for food manufacture (refer to Annex 1)

Therefore, we strongly recommend that CODEX change the document as outlined below to revoke the text that raises unwarranted safety concerns of enzymes and publish an erratum to the effect. The assertion that lipases, amylases, and proteases are generally used as processing aids should be sufficient rationale to support the proposed discontinuation of the respective INS numbers.

The following changes are requested by AMFEP:

- Preferably change the following:

10. Amylases (INS 1100 i, ii, iii, iv, v, vi), proteases (INS 1101 i, ii, iii, iv, v, vi), lipases (INS 1104) are ~~not justified for use as food additives since they fall outside the scope of the definition for~~ deleted because they are not used as food additives. These substances have no activity in final food (flour and bakery products) because the production process typically includes heat inactivation of the enzyme in order to terminate the process when the desired effect is obtained.

- Delete the following:

~~11. In compliance with table 3 of GSFA, amylases (INS 1100 i, ii, iii, iv, v, vi), proteases (INS 1101 i, ii, iii, iv, v, vi) and lipases (INS 1104) could be used in broad food categories in accordance with GMP. In some of these FC activity enzymes could be manifested.~~

~~12. Amylases (INS 1100 i, ii, iii, iv, v, vi), proteases (INS 1101 i, ii, iii, iv, v, vi) and lipases (INS 1104) are digestive enzymes. They have been broadly used in therapy of digestive tract diseases. However in case of systematic use of digestive enzymes with food there could be imbalance in digestive process:~~

~~Decrease production of endogenic digestive enzyme~~

~~Change of Michaelis constant, from which depend of enzymatic reaction rate in the digestion of food~~

~~Violation allostiric control of enzyme activity~~

~~Hormone imbalance which arefor supervising production of digestive enzyme responsible in the human organism.~~

[5] http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FMeetings%252FCX-711-49%252FWD%252Ffa49_12e.pdf

~~13. For example, changing quantity of lipase and amylase could lead to imbalance of endocrine function of pancreas and lowering organism tolerance into glucose. It should be noted that:~~

~~As producers of these food additives permitted microorganisms with modified DNA~~

~~Volumes of enzymes production and food producedwith help of enzymes are constantly increased.~~

~~14. Produced by GM microorganisms enzymes could have different characteristics from enzymes elaborated in digestive tract:~~

~~Another optimum of temperature and pH for enzyme activity~~

~~Different enantiomeres could have different type of enzyme activity.~~

~~15. For example, the possibility of negative influence of food additive lipase (in case its use in a higher concentration) showed in:~~

~~WHO Food Additives Series: 71, World Health Organization, Geneva, 2015, p.27-37;~~

~~Safety evaluation of certain food additives World Health Organization, Geneva, 2012. p.39-51;~~

~~Safety evaluation of certain food additives World Health Organization, Geneva, 2012. p. 51-63;~~

~~Sixty-firstreportoftheJointFAO/WHO Expert Committee on Food Additives, WHO 2004, 15-20.~~

ANNEX 1 - AMFEP Justification
General Safety of Microbial Enzymes used in Food Processing

1. Enzymes are inherently present in common foods such as fruits, vegetables, dairy, meat, fish, eggs and grains.

Thereby, enzymes are normally ingested by humans and animals in their active state (in raw food) or as inactive proteins (in cooked or processed food). The fact that enzymes are regarded as “intrinsically safe” based on several years of testing, use in commerce and an in-depth knowledge of their properties (Olempska-Beer et al., 2006) is well-established. Enzymes are proteins and ingested proteins don’t typically represent a hazard. Protein is an essential part of the diet. Proteins are relatively large and labile and our digestive systems have evolved to convert protein to its building blocks for incorporation into our bodies.

2. Thorough Enzyme safety assessments.

Enzymes are commonly used in processing of food and production of food ingredients (e.g., baking, starch processing, fruits and vegetables processing, dairy production, brewing) and in unlocking nutrients (e.g., energy, amino acids, phosphorous) in animal feeds. A typical enzyme safety evaluation such as what is done to satisfy GRAS (Generally Recognized As Safe) requirements, takes into account the five main elements for safety evaluation- enzyme/protein safety, production strain safety, safety of manufacturing process, toxicological studies and exposure assessment (Sewalt et al., 2016) and this provides a robust framework to FDA, EFSA, and other agencies for enzyme safety assessment.

3. Elimination and removal of toxins

As part of enzyme characterization, screening for protein homology to toxins and allergens is conducted during product development, using *in silico* tools and established allergen and protein toxin databases. This eliminates the inclusion of any known toxin or allergen sequences in the product. Further, enzymes have very low toxicity potential as demonstrated in various acute, sub-chronic, and genotoxicity studies for enzymes from production organisms that are traditionally derived (Pariza and Foster, 1983), genetically engineered (Pariza and Johnson, 2001), including for protein-engineered enzymes (Pariza and Cook, 2010) as summarized in the above publications. The plethora of data from multiple toxicological tests, use of established Safe Strain Lineages (SSL), the consistent use of well-accepted molecular techniques to transform and characterize the genetically engineered strains, adherence to current food Good Manufacturing Practices (cGMP), and finished product specifications defined by the FAO/WHO Joint Evaluation Committee for Food Additives (JECFA, 2006) and in the latest edition of the Food Chemical Codex (US Pharmacopeia, 2016)], all contribute to the unequivocal establishment of the safety of food enzymes (Sewalt et al. 2016).

4. Proteins are readily metabolized to its basic amino acid components

Per the Endocrine Society, the world’s authoritative scientific association of clinical and research endocrinologists, an endocrine-disrupting chemical (EDC) is an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action (Diamanti-Kandarakis et al., 2009). In contrast to #13 of the document prepared by the chair of the EWG, there is no evidence in the scientific literature indicating that protein enzymes are endocrine disruptors. In fact, as noted above, proteins are readily metabolized by our digestive systems to its basic amino acid components for incorporation into our

bodies. And hence #12 of the document of the chair of the EWG is also quite contrary to the physiological processes of the human body.

5. Safe level of enzyme exposure

#10 of the EWG analysis and recommendations rightly states, “These substances (enzymes) have no activity in final food (flour and bakery products) because the production process typically includes heat inactivation of the enzyme in order to terminate the process when the desired effect is obtained.” Therefore, the low levels of enzyme usage in food processing and their further removal by processing through heating and digestion ensures that exposure levels to the consumer are much below and in line with what is stated in the JECFA safety evaluation references for amylases, lipases and proteases quoted by the eWG under #15 (JECFA reports 2004, 2012 and 2015).

References:

Diamanti-Kandarakis E, Bourguignon J-P, Giudice, LC, Hauser R, Prins GS, Soto AM, Zoeller RT, Gore AC (2009). “Endocrine-Disruption Chemical: An Endocrine Society Scientific Statement”. Endocr Rev. 30 (4): 293-342.

Evaluation of certain food additives and contaminants. Sixty-first report to the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization, Geneva, 2004, 15-20.

JECFA (Joint Evaluation Committee of Food Additives), 2006. General specifications and considerations for enzyme preparations used in food processing. In: Compendium of food additive specifications, volume 4. Analytical methods, test procedures and laboratory solutions used by and referenced in the food additive specifications. pp. xxi-xxv. FAO/JECFA Monographs 1. Rome

Olempska-Beer ZA, Merker RI, Ditto MD, DiNovi MJ (2006). “Food-processing enzymes from recombinant microorganisms--a review”. Regul Toxicol Pharmacol. 45:144-158.

Pariza, MW and Foster, EM (1983). “Determining the Safety of Enzymes Used in Food Processing”. J. Food Prot. 46: 453-468.

Pariza MW and Johnson EA (2001). “Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century”. Regul Toxicol Pharmacol. 33, 173-186.

Pariza, MW and Cook, M (2010). “Determining the safety of enzymes used in animal feed”. Regul Toxicol Pharmacol. 56, 332-342.

Safety evaluation of certain food additives and contaminants. Prepared by the Seventy-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva, 2012.- p.39-51.

Safety evaluation of certain food additives and contaminant. Prepared by the Seventy-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva, 2012.- p. 51-63.

Safety evaluation of certain food additives and contaminants. Prepared by the eightieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva, 2015, p.27-37.

Sewalt, V, Shanahan, D, Gregg, L, La Marta, J, and Carillo, R (2016). “The Generally Recognized As Safe (GRAS) Process as Catalyzed by Industrial Microbial Enzymes”. Industrial Biotechnology. 12 (5) 295-302.

U.S. Pharmacopeia (2016) Monograph: Enzyme Preparations. In: Food Chemicals Codex, 10th Edition. Washington, D.C.

Enzyme Technical Association (ETA)

The Enzyme Technical Association (“ETA” or “Association”) is a trade association that represents manufacturers and marketers of enzyme products in North, Central, and South America. It has been in existence since 1970 and maintains an active role in assisting in the development of regulations and policies that affect the enzyme industry. ETA represents the majority of the enzyme product industry in the Americas.

The Association has become aware of the CODEX Proposed Draft Revision to the International Numbering System (“INS”) for Food Additives (CAC/GL 36-1989). Of particular interest to the ETA is that the proposal includes the removal of INS numbers for three categories of enzymes (lipases, amylases, and proteases), while also erroneously suggesting safety issues with these enzymes. All three have been accepted as suitable for use in foods in the Codex General Standard for Food Additives (GSFA) for many years. As a result, ETA submits the important comments below confirming the safety of enzymes listed, and strongly recommends that CODEX remove the language which suggests enzymes are not safe.

1. Enzymes are inherently present in common foods such as fruits, vegetables, dairy, meat, fish, eggs and grains. Enzymes are commonly used in processing of food and production of food ingredients (e.g., baking, starch processing, fruits and vegetables processing, dairy production, brewing) and in unlocking nutrients (e.g., energy, amino acids, phosphorous) in animal feeds. The fact that enzymes are regarded as "intrinsically safe" based on a significant number of years of testing, a long history of safe use in food , and an in-depth knowledge of their properties (Olempska-Beer et al., 2006) is well-established.

2. A typical premarket enzyme safety evaluation takes into account all essential elements for safety including enzyme/protein safety, production strain safety, safety of manufacturing process, toxicological studies and exposure assessment (Sewalt et al., 2016). As part of the safety assessment, enzymes have been subjected to a number of toxicological studies, and have been shown to be practically non-toxic (Pariza and Foster, 1983) (Pariza and Johnson, 2001) (Pariza and Cook, 2010).

3. Enzymes are proteins that are readily metabolized into their basic amino acid components, and do not pose any health concerns. There is no evidence in the scientific literature to show, for example, that enzymes are endocrine disruptors, as alluded to in #13 of the document prepared by the chair of the EWG. Enzymes when used as processing aids are also not active in the final food, let alone active in the human consuming the food. In addition, the use of enzymes as processing aids in foods have been fully reviewed by JECFA for safety, with no safety concerns raised (JECFA reports 2004, 2012 and 2015).

In closing, ETA would like to thank you for taking our comments into consideration to prevent the inaccuracies in this proposal from being included in the final report. We further strongly encourage the final report to include a statement that says that the removal of these INS numbers for protease, amylase, and lipase enzymes used as processing aids is not based on any safety concern.

REFERENCES

Evaluation of certain food additives and contaminants. Sixty-first report to the Joint FAO/WHO Expert Committee on Food Additives, World Health Organization, Geneva, 2004, 15-20.

Olempska-Beer ZA, Merker RI, Ditto MD, DiNovi MJ (2006). "Food-processing enzymes from recombinant microorganisms--a review". Regul Toxicol Pharmacol. 45:144-158.

Pariza, MW and Foster, EM (1983). "Determining the Safety of Enzymes Used in Food Processing". J. Food Prot. 46: 453-468.

Pariza MW and Johnson EA (2001). "Evaluating the safety of microbial enzyme preparations used in food processing: update for a new century". Regul Toxicol Pharmacol. 33, 173-186.

Pariza, MW and Cook, M (2010). "Determining the safety of enzymes used in animal feed". Regul Toxicol Pharmacol. 56, 332-342.

Safety evaluation of certain food additives and contaminants. Prepared by the Seventy-sixth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva, 2012.- p.39-63.

Safety evaluation of certain food additives and contaminants. Prepared by the eightieth meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), World Health Organization, Geneva, 2015, p.27-37.

Sewalt, V, Shanahan, D, Gregg, L, La Marta, J, and Carillo, R (2016). "The Generally Recognized As Safe (GRAS) Process as Catalyzed by Industrial Microbial Enzymes". Industrial Biotechnology. 12 (5) 295-302.

EU Specialty Food Ingredients

EU Specialty Food Ingredients, formerly ELC, would like to comment on the following topics:

- **Proposed deletion of Nisin (INS 234) and Natamycin (Pimaricin, INS 235) from the INS list**[6]

The allegation is made in the document according to which these substances were antibiotics and a connection is also made with Antimicrobial resistance (AMR). It is then proposed that Nisin and Natamycin (Pimaricin) be deleted from the INS list as this could help solve the problem of AMR.

EU Specialty Food Ingredients fully supports the adoption of any appropriate and effective measures aiming to reduce AMR.

We also note that INS 234 and 235 are presently permitted in the Codex General Standard for Food Additives (GSFA)[7] as preservatives for use in certain applications such as dairy, meat and bakery products.

[6] See paragraphs 16 to 18 and Annex 1 Table 2 of CX/FA 17/49/12.

[7] See http://www.fao.org/fao-who-codexalimentarius/standards/gsfa/en/

According to their Joint FAO/WHO Expert Committee on Food Additives (JECFA) Monographs, INS 234[8] is an antimicrobial preservative and INS 235[9] a fungicidal preservative. According to the *Class Names and the International Numbering System for Food Additives* (CAC/GL 36-1989)[10], the functional class 21 "Preservatives" includes the following technological purposes: preservative, antimicrobial preservative, anti-mycotic agent, fungistatic agent, etc.

In our view, INS 234 and 235 serve those purposes and rightly belong to this established technical class of food additives.

We would also like to point out that Natamycin (INS 235) was evaluated in the European Union for use as a food additive by the European Food Safety Authority (EFSA) in 2009 (EFSA Journal 2009; 7(12):1412)[11] and that AMR was included in that evaluation. We note that EFSA concluded for Natamycin: *"…that there was no safety concern for the induction of antimicrobial resistance."* Likewise, EFSA concluded for the use of Nisin as a food additive (EFSA Journal (2006) 314, 1-16)[12] *"…that the development of antibiotic resistance is not of concern in relation to use of Nisin in food".*

From a procedure standpoint, in case a Codex member is aware of any new available data that would question the safety of an additive or its legitimate use according to the GSFA requirements - in particular section 3 thereof, processes are in place to get those data evaluated by JECFA and discussed by the CCFA. Therefore, should there be any concerns of that kind; we wonder whether they should be addressed through the update of the INS list in the first place. In particular, the proposal at stake made via the INS electronic working group is a request to revoke the existing provisions for these two food additives.

Besides, risk assessment is not within the mandate of the INS electronic working group (e-WG), and Codex procedure dictates that Committees are to defer to their designated risk assessment bodies when making risk management decisions. As such, EU Specialty Food Ingredients is of the opinion that the reasons behind the INS e-WG proposals for Nisin and Natamycin (Pimaricin) are not valid given the e-WG's scope and authority.

Overall, EU Specialty Food Ingredients strongly objects to the proposed deletion of INS 234 and 235 from the INS list and suggests that the appropriate Codex procedure to obtain the revocation of food additives provisions, if justified, is clarified by the Committee Chair or CCFA secretariat.

- **Working document comments relating to enzymes (see paragraphs 10 to 15)**

With regard to the proposed deletion of deletion of amylases (INS 1100 i, ii, iii, iv, v, vi), proteases (INS 1101 i, ii, iii, iv, v, vi) and lipases (INS 1104) in the INS list, EU Specialty Food Ingredients fully supports the comments submitted by Amfep on the Codex working document CX/FA 17/49/12.

International Association of Color Manufacturers (IACM) and Natural Food Colours Association (NATOL)

IACM and NATCOL continue to supports the addition of elderberry color and hibiscus color to the INS and re-confirms that these colors are both anthocyanins, and are appropriately categorized as sub codes of INS 163. However, we respectfully submit that the appropriate INS Number for Elderberry color should be 163(ix) instead of 163(iv) as listed in CX/FA 17/49/12.

IACM and NATCOL appreciate the opportunity to provide comments at Step 3.

International Food Additives Council (IFAC)

The International Food Additives Council (IFAC) is responding to the request for comments found in the Codex Committee on Food Additives (CCFA) document: "PROPOSED DRAFT REVISION TO THE INTERNATIONAL NUMBERING SYSTEM (INS) FOR FOOD ADDITIVES (CAC/GL 36-1989)" (CX/FA 17/49/12, December 2016). The comments that follow address the proposals in Annex 1 of that document to remove nisin (INS 234) and pimaricin (natamycin) (INS 235) from the INS list.

[8] See http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/monograph14/additive-295-m14.pdf
[9] See http://www.fao.org/fileadmin/user_upload/jecfa_additives/docs/Monograph1/Additive-293.pdf
[10] See http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B36-1989%252FCXG_036e.pdf
[11] See https://www.efsa.europa.eu/fr/efsajournal/pub/1412
[12] See https://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/314.pdf

Position:

IFAC opposes the INS electronic working group's (eWG) proposal to delete nisin (INS 234) and pimaricin (natamycin) (INS 235) from the INS list on the grounds that removal of these substances from the INS list and, by consequence removal of adopted provisions for the materials in existing Codex Standards, could help address the problem of antimicrobial resistance (AMR). First and foremost, we do not believe that the existing safety evaluations of these materials conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), the designated risk assessment body for CCFA, indicate an AMR concern when these materials are used in foods. As a result, we do not believe that the stated end goal of removing them from the INS list will have any impact on reducing instance of AMR.

As explained in much greater detail below, AMR concerns were specifically reviewed when both of these materials were evaluated by JECFA, and JECFA found AMR not to be of concern when the substances are used in food in accordance with conditions specified in the General Standard for Food Additives (GSFA) and in accordance with good manufacturing practice (GMP). Risk assessment is not within the mandate of the INS eWG, and Codex procedure dictates that Committees are to defer to their designated risk assessment bodies when making risk management decisions. As such, IFAC is of the opinion that the reasons behind the INS eWG proposals for nisin and pimaricin (natamycin) are not valid given the eWG's scope and authority. Furthermore, we are of the opinion that the proposals are not consistent with the JECFA (CCFA's designated risk assessment body) conclusions on these materials. For these reasons, we call on CCFA to reverse the INS eWG recommendation and ensure that nisin and pimaricin (natamycin) are not removed from the INS list.

Background:

When microorganisms (such as bacteria, fungi, viruses, and parasites) are exposed to clinical antimicrobial drugs (such as antibiotics, antifungals, antivirals, antimalarials, and anthelmintics), they may naturally develop resistance to these treatments over time, usually through genetic changes. The World Health Organization (WHO) has noted that misuse and overuse of these clinical antimicrobials is accelerating this process. Microorganisms that develop antimicrobial resistance are tolerant to the medicines used in treatment, rendering them ineffective for their therapeutic indication. This allows infections to persist in the body and increases the risk of spread to others. [13]

IFAC agrees that all stakeholders in the food value chain must strive to reduce possible causes of AMR. However, decisions about what practices to implement and what materials to avoid to reduce AMR must be guided by scientific evidence and widely accepted risk assessment principles.

Natamycin (INS235): JECFA's review and conclusions

The emergence of resistance to antimicrobials was a known concern when JECFA re-evaluated the safety of natamycin (INS 235) in 2001. Thus, JECFA specifically requested "All relevant information relating to toxicity, (with specific consideration to increase microbial resistance)..." and critically evaluated the possible development of resistance among microflora as a consequence of exposure to natamycin. Their findings and conclusions, published in the JECFA toxicology monograph and the WHO technical report, are summarized below:[14,15]

- The use of natamycin as an antifungal agent in food may result in exposure of the indigenous flora to trace quantities of antimicrobial residues.
- The Committee concluded that natamycin would not have an effect on bacteria in the human gastrointestinal tract as bacteria are not affected by polyenes, and that disruption of the barrier to colonization of the intestinal tract was therefore not a concern.
- Selection of natamycin-resistant fungi was not considered an issue as fungi are much less prevalent than bacteria in the human gastrointestinal tract, and acquired resistance in fungi was not observed in related studies.

The conclusions reached by JECFA and their decision to confirm the existing ADI for natamycin affirms that natamycin, when used as a food preservative consistent with conditions specified in the GSFA and in accordance with good manufacturing practices, does not pose a meaningful risk to fostering the development of significant antimicrobial resistance or any other safety concerns.

---

[13] WHO Factsheet: Antimicrobial resistance (http://www.who.int/mediacentre/factsheets/fs194/en/); September 2016

[14] JECFA Toxicology Monograph (2001): Natamcyin (http://www.inchem.org/documents/jecfa/jecmono/v48je06.htm#2.2.7.2)

[15] WHO Technical Report Series 909: Fifty-seventh report of the Joint FAO/WHO Expert Committee on Food Additives; §3.1.6.1 Natamycin (Pimaricin); pp 25-29 (http://apps.who.int/iris/bitstream/10665/42578/1/WHO_TRS_909.pdf)

Nisin (INS234): JECFA's review and conclusions

JECFA re-evaluated nisin (INS 234) safety in 2013[16]. The development of resistance resulting from the consumption nisin in foods was specifically reviewed. The JECFA toxicology monograph highlights various studies aimed at assessing whether nisin consumption could lead to the development of nisin-resistant bacteria. Specifically, JECFA examined whether nisin could alter the nature of the bacterial flora in the oral cavity and/or if sub-lethal concentrations of nisin present in food could induce the development of nisin resistance in foodborne microbes or cross-resistance to 17 commonly used therapeutic antibiotics. The Committee noted that its review of the existing body of literature indicated the following:

- The residence time of nisin in the mouth is too short to permit the development of resistance.
- Ingested nisin is inactivated by pancreatic α-chymotrypsin in the upper part of the intestinal tract; no biologically active nisin was detected in the colon or caecum of rats.
- No evidence of the cross-resistance development to the 17 commonly used therapeutic antibiotics studied by Hossack et al (1983).

Based upon their critical evaluation of available safety and toxicological data, including information specifically relating to resistance development, JEFCA raised the ADI for nisin to 2 mg/kg bw. This action clearly indicates that the Committee had no safety concerns relating to the development or transmission of antimicrobial resistance when nisin is used as a food preservative, in a manner consistent with conditions specified in the GSFA and in accordance with good manufacturing practice.

Conclusion:

For the reasons explained above, IFAC believes that CCFA should reject the INS eWG proposal to remove nisin (INS 234) and pimaricin (natamycin) (INS 235) from the INS list based on the presumption that removing them will reduce the potential for AMR. Independent review by JECFA affirms that the use of nisin and natamycin as food preservatives do not present any significant concerns associated with the development of antimicrobial resistance and the resulting loss in effectiveness of clinical/therapeutic antimicrobials. As JECFA is the risk assessment body to which CCFA must defer and because risk assessment is not within the mandate of the INS eWG, IFAC believes that CCFA must reject the recommendation and ensure that both of these materials remain on the INS list.

[16] WHO Food Additives Series 68: Seventy-seventh report of the Joint FAO/WHO Expert Committee on Food Additives; Nisin; pp 91-114 (http://apps.who.int/iris/bitstream/10665/99070/1/9789241660686_eng.pdf)