INDUSTRY GUIDANCE DOCUMENT[1]

Executive Summary

This document is an industry Guidance prepared by interested European industry stake-holders convened under the auspices of the informal "Amino Acid Coalition". The Guidance is intended to provide a voluntary and self-regulating basis for the safe nutritional use of amino acids, and their specific derivatives, in food supplements and other foods. It comprises a description of the current regulatory situation, a list of substances proposed, accompanied with relevant specifications and best practices.

Scientific and Regulatory Background

Amino acids are evolutionarily ancient organic compounds containing amino (-NH2) and carboxyl (-COOH) functional groups, along with a side chain specific to each amino acid. Hundreds of amino acids and derivatives are known in nature, although only twenty amino acids make up human proteins. Nine amino acids are nutritionally essential and several other amino acids are considered conditionally essential.

Amino acids as substances added to foods[2] including specialized nutrition products and food supplements[3] are in the scope of EU food law. Some EU Member States have in addition established more detailed country-specific rules on the addition of amino acids for nutritional or other non-technological purposes. Despite the principle of mutual recognition, those national rules can in practice impede the free movement of food supplements and

[1] Disclaimer: The information contained herein does not constitute legal or other professional advice. No member of the involved industry associations accepts any responsibility or liability to users or any third parties in relation to the use of the information contained in this guidance.

[2] Recital 1 of Regulation (EC) 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods, as clarified by the Judgment of the Court of 19 January 2017 Queisser Pharma GmbH & Co. KG v Bundesrepublik Deutschland.

[3] Recital 6 of Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

other foods containing added amino acids that can legally be traded in other EU Member States, preventing consistent and effective controls on quality and specifications for amino acids added or fortified, creating unequal conditions of competition, and thus having a direct impact on the functioning of the internal market. Some of the problems were reflected in the Judgment of the Court of Justice of the European Union (CJEU) of 19 January 2017 in Case C-282/15 of Queisser Pharma GmbH vs. Bundesrepublik Deutschland.

Moreover, significant changes in the relevant EU regulatory framework have taken place since July 2016. The addition of amino acids to Foods for Particular Nutritional Uses (PARNUTS) was formerly permitted under Directive 2009/39/EC, with a detailed list of permitted chemical forms in Regulation (EC) 953/2009[4]. With the repeal of Directive 2009/39/EC, only Foods for Specific Groups (FSG), now governed by Regulation (EU) 609/2013[5] (FSG Regulation) which entered into force in July 2016, have a clear set of rules for the use of amino acids and their derivatives in such foods, because the FSG Regulation established a Union list of substances (including amino acids) which may be added to the FSG categories. This Union list can be updated following the delegated procedure in accordance with article 16 of the FSG Regulation. For substances included in this Union list for which purity criteria are not established by Union law applicable to food, generally acceptable purity criteria recommended by international bodies shall apply. All other foods including other specialized nutrition products, such as meal replacements for weight control or foods intended for sportspeople and, food supplement products, fall under the horizontal rules of general EU food law and for these food categories the substance used should also comply with generally acceptable purity criteria recommended by International Bodies. Use of amino acids and their derivatives should generally be accepted if the amino acid or its derivative is safe for human consumption and does not fall under the novel food category established by the Commission Implementing Regulation (EU) 2017/2470 setting up the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods.

Taking into account the above mentioned EU regulatory framework, food business operators (FBOs) in Europe are adding amino acids and their derivatives to foods for a number of nutritional purposes, among others, to restore their content where this has been reduced during manufacturing or handling procedures. In view of the complex EU regulatory framework described above and the differentiation of legal provisions impacting amino acid use in food across the EU, the “Amino Acid Coalition” has sought to clarify and identify the amino acids and those selected derivatives for which the Coalition members provided appropriate purity standards and that have a history of use in nutrition.

[4] Commission Regulation (EC) 953/2009 of 13 October 2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses.

[5] Regulation (EU) 609/2013 on food intended for infants and young children, food for special medical purposes, and total diet replacement for weight control.

Proposed Table of Amino Acids and their Derivatives

The proposed listing of amino acids and derivatives for food use (below) is based on a history of use, existence of appropriate purity standards, the best practices of the relevant industries, as well as the practical nutritional needs in food supplements and food formulations. Suggestions were also derived from the regulatory precedent which came into existence in November 2016 in Denmark[6].

Key Concepts in Composing the Table of Amino Acids and their Derivatives

i. Forms of amino acids

Amino acids are characterized by a high degree of structural flexibility because of their conformational freedom; as well as by chemical versatility because they can act as either bases or acids. Therefore, various forms of amino acids exist in nature or are produced through fermentation, enzymatic or chemical methods. Amino acids have diverse organoleptic properties, physical appearance and stability but not significantly different nutritional values, or metabolic pathways in the human body.

Therefore, this Guidance includes not only the free L-forms of amino acids, but also their hydrated and anhydrous forms, salts of two amino acids, keto, Na, Ca, K, Zn, Mg, NH_4+, as well as HCl forms. A risk assessment/management precedent does exists because various forms of glutamates were grouped into a single category of "flavor enhancers" (E 620-625) and their safety evaluation was conducted as if they represented a single compound.

Moreover, Regulation (EC) 1333/2008[7] exempts "amino acids and their salts" from the definition of food additives when they do not have a technological function. Similar precedents exist for several mineral salts of lysine and of aspartic acid, and for some salts of an acidic with a basic amino acid. In addition, some other amino acid derivatives are listed in the FSG Regulation or other food regulations set at national level.

ii. Specifications (monographs)

EU food law does not stipulate purity criteria for amino acids, with the exception of amino acids used in FSG, where, in the absence of specific legal provisions, specifications set in Regulation (EU) 231/2012[8] apply (where they exist). Such specifications, as highlighted below, are generally regarded as insufficient.

Purity standards and specifications are the main determinants of amino acid safety in human nutrition. All FBOs, including suppliers of amino acids for food use and

[6] BEK nr 1398 af 28/11/2016 (Bekendtgørelse om tilsætning af visse andre stoffer end vitaminer og mineraler) URL: https://www.retsinformation.dk/pdfPrint.aspx?id=185066

[7] Regulation (EC) 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives.

[8] Commission Regulation (EU) 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) 1333/2008 of the European Parliament and of the Council.

manufacturers of food products for the final consumer, are responsible for ensuring product safety under EU law. When safety is ensured, FBOs may choose between appropriate quality specifications. On this basis, the Guidance is referring two sets of specifications (monographs); the Food Chemical Codex (FCC) and European Pharmacopeia (EP), both in their current versions.

The FCC is a compendium of internationally recognized standards for the identity, purity, and quality of food ingredients used in international commerce. It was originally published by the US Institute of Medicine. In 2006, publication of the FCC was assumed by USP, a not-for-profit, science-based, non-governmental standards-setting organization. On the other hand, the EP is a single European reference compendium for quality control of raw materials used in the production of medicines, intermediates of synthesis, and in final medicines.

Factual comparison of the FCC and EP monographs, which was conducted by the "Amino Acid Coalition" during Nov. 2017 – Jan. 2018, indicated that their appearance and chemical identification are given in more detail in the EP than in the FCC monographs. Some typical contaminants covered by EP, but not by FCC monographs, are: chlorides, sulphates, ammonium and iron. On the other hand, limits for general parameters, like loss on drying, sulphated ash or content (assay), are often identical or differ only slightly between the two monographs. Importantly, heavy metals are not listed in the EP monographs because impurity management in the pharmaceutical area must comply with ICHQ3D purity guidelines.

At this stage, it is important to notice that this Guidance is not to be interpreted as an endorsement of one set of specifications over another. There are several internationally-recognized organizations that have responsibility for establishing specifications (monographs) for food ingredients including JECFA. Regardless of which organization performs the evaluation, the specifications established should ensure the safety and quality of food products manufactured with these ingredients. As described in the general principles of the FCC, ingredient specifications "*are designed to ensure that food ingredients have the specified identity and a sufficiently high level of quality to be safe under usual conditions of intended use in foods or in food processing*". Because the objectives are always the same, namely to ensure that food ingredients have sufficient quality and are safe, differences in the specifications should not be interpreted as deficiencies. Instead, the specifications established by these different, internationally-recognized, organizations should be viewed as equivalent in terms of ensuring the quality and safety of food ingredients. It is the responsibility of suppliers of amino acids intended for food use to determine such equivalence.

iii. Other specifications (monographs)

Because free amino acids have technological properties and taste, some of them are authorized as food additives, notably L-glutamates (E620-625), glycine (E640), L-leucine (E641) and L-cysteine (E920). For these substances, when used as food additives, the EU

food law already determines appropriate specifications (Regulation (EU) No 231/2012). However, the food additive specifications apply to use of the substance for one or more of the technological functions applicable to food improvement agents; limited food categories; and use only in quantities necessary to achieve the required technological effects. While those specifications apply legally to FSG Regulation (Recital 37), they may not be the most appropriate purity standards for nutritional applications in diverse food matrixes, and should be seen as minimum standards to be complemented with further specifications.

Finally, for those amino acids/derivatives for which neither the EP nor the FCC monographs exist, the members of the "Amino Acid Coalition" committed to providing internal specifications (monographs), as indicated in the below table, as examples of in-house specifications.

iv. Requirements for FBOs

FBOs at all stages of production, processing and distribution within the businesses under their control shall ensure that foods satisfy the requirements of food law which are relevant to their activities and shall verify that such requirements are met.

It is therefore the joint responsibility of the FBOs along the food chain to ensure full compliance with food law. This includes a requirement to source ingredients, including amino acids/derivatives, only from manufacturers with food safety procedures based on Hazard Analysis and Critical Control Points (HACCP), in accordance with current Good Manufacturing Practice (GMP), equivalent to those foreseen under EU law, and, when produced in the EU, in accordance with the Food Hygiene Regulation (EC) 852/2004[9] in establishments registered under that Regulation. Moreover, it is also the responsibility of the FBOs placing amino acids, and products which contain them, on the EU market to ensure full compliance with Regulation (EU) 2015/2283 on novel food/food ingredients. "Novel food" means any food that was not used for human consumption to a significant degree (in the EU) before 15 May 1997, and that falls under a category of novelty as indicated in the Regulation.

[9] Regulation (EC) 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of food additives.

Non-exhaustive table of amino acids/derivatives[11]

	Identity and purity specifications		
Amino Acids[10]	European Pharmacopeia (EP)	Food Chemical Codex (FCC)	Other
L-alanine	✓	✓	
L-arginine	✓	✓	
L-asparagine		✓	
L-aspartic acid	✓	✓	
L-citrulline		✓	
L-cysteine		✓	E 920
L-cystine	✓	✓	
L-histidine	✓	✓	
L-glutamic acid	✓	✓	E 620-625
L-glutamine		✓	
glycine	✓	✓	E 640
L-isoleucine	✓	✓	
L-leucine	✓	✓	E 641
L-lysine	✓	✓	
L-methionine	✓	✓	
L-ornithine			in-house (available on request)
L-phenylalanine	✓	✓	
L-proline	✓	✓	
L-serine	✓	✓	
L-threonine	✓	✓	
L-tryptophan	✓	✓	
L-tyrosine	✓	✓	
L-valine	✓	✓	
D,L-methionine		✓	
Derivatives	European Pharmacopeia (EP)	Food Chemical Codex (FCC)	Other
L-arginine-L-pyroglutamate			in-house (available on request)
N-acetyl-L-methionine		✓	
L-carnitine		✓	
taurine		✓	
L-lysine acetate	✓		in-house (available on request)
creatine		✓	in-house (available on request)
beta-alanine			in-house (available on request)

Brussels, 25th September 2018

[10] Individual amino acids in the free, hydrated or anhydrous forms, or as salt of two amino acids, keto, Na, Ca, K, Zn, Mg, NH_4+, HCl forms

[11] Internal purity criteria provided by a member of the Coalition will be available upon request.

European Specialist Sports Nutrition Alliance (ESSNA) is a pan-European trade association representing the interests of the sports nutrition sector across Europe. Our members are large global businesses, smaller specialist brands, suppliers of ingredients, sports nutrition retailers, companies representing multi sports nutrition brands, as well as national associations. ESSNA's main aim is to campaign for appropriate policy and regulation for sports nutrition products in Europe, as well as to improve the reputation of the sector with regulators and the public. We do so by working to improve consumer knowledge of sports nutrition products and the industry. ESSNA is a CODEX Observer and a registered EFSA stakeholder.

The European Federation of Associations of Health Product Manufacturers (EHPM) was created in 1975 and represents approximately 1,600 health-product manufacturers in 13 European countries. Through our member associations we aim to provide consumers with safe, science-based, high quality products as well as accurate and helpful information about their nutritional value and use. Over 90% of the companies that are members of EHPM through our national associations are SMEs. EHPM's focus is very much on securing a workable regulatory structure for these companies."

European Vegetable Protein Association (EUVEPRO) represents the interests of manufacturers and distributors of vegetable proteins for human consumption (food) in the European Union. EUVEPRO monitors legislation that affects plant protein ingredients manufacturers, suppliers and users in Europe. It identifies potential issues specific to the sector, and delivers technical input and positions to EU decision makers as well as international bodies. EUVEPRO is a valued partner by the institutions and stakeholders of related industries, and promotes further recognition in European, national and international legislation, of vegetable protein products as foodstuffs and ingredients in their own right.

Food Supplements Europe (FSE) has been created to represent the interests of the European food supplement sector. Its membership includes national associations and companies committed to ensuring that future EU legislation and policy reflects the important role that this sector plays in the health of consumers. The scope of its work covers food supplements and food supplement ingredients, including vitamins, minerals, other substances and botanicals.

International Council on Amino Acid Science (ICAAS) is a world-wide non-profit scientific association focused on amino acid toxicology; and on helping to ensure the safety, quality and efficacy of amino acid used in human nutrition. ICAAS is an observer organization of Codex Alimentarius. ICAAS sponsors clinical research, organizes regular "Amino Acid Assessment Workshops" which are published in J. Nutrition, and monitors the use of amino acids in human nutrition world-wide.

Specialised Nutrition Europe (SNE) is the trade association representing the interests of the specialised nutrition industry across Europe. SNE members are the national associations of 19 European countries including a majority of EU states and their members are the companies producing tailor made dietary solutions for populations with very specific nutritional needs. These include: infants and young children, patients under medical supervision, sportspeople, overweight and obese consumers, and those suffering from coeliac disease.