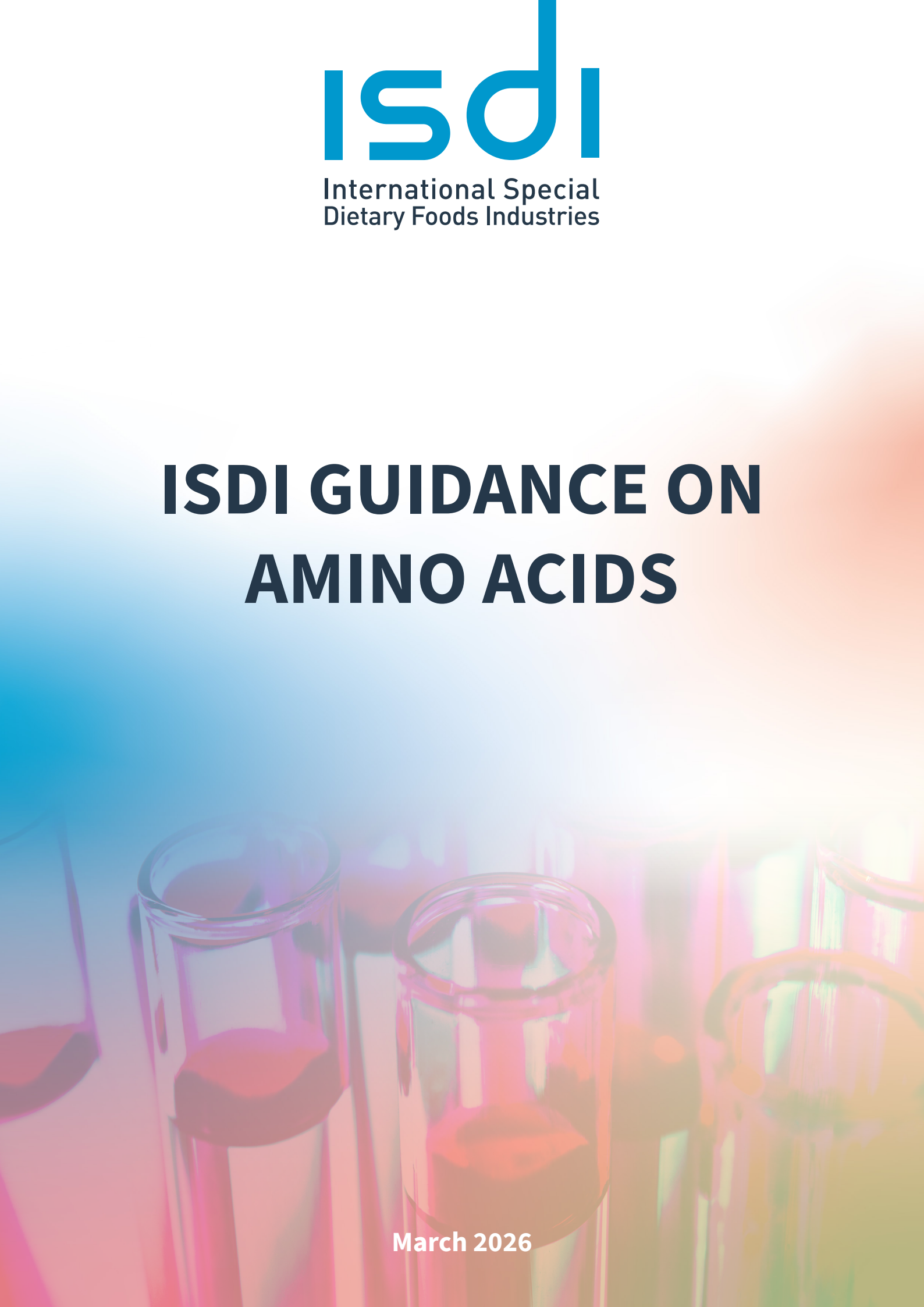
International Special Dietary Foods Industries

ISDI GUIDANCE ON AMINO ACIDS



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► A summary of purity requirements and permitted amino acids for use in FSDU according to national regulations is published separately in Annex II, a standalone ISDI document.

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This guidance provides a voluntary and self-regulating framework to support the safe and nutritionally appropriate use of amino acids and their specific derivatives in Foods for Special Dietary Uses (FSDU). It is intended to assist Food Business Operators (FBOs) in understanding the Codex Alimentarius framework as it relates to amino acids, including a proposed list of substances, relevant specifications, and recommended best practices. This document does not supersede national regulations, which must be confirmed by FBOs prior to marketing products with added amino acids.

SCIENTIFIC AND REGULATORY BACKGROUND

Amino acids are evolutionary ancient organic compounds characterized by the presence of amino (-NH2) and carboxyl (-COOH) functional groups, along with a side chain (-R) unique to each amino acid. While hundreds of amino acids and derivatives exist in nature, only twenty amino acids serve as the building blocks of proteins in the human body.

Of these, nine amino acids are nutritionally essential, meaning they cannot be synthesized by the body and must be obtained through the diet. In contrast, four amino acids can be synthesized and are thus classified as non-essential. The remaining amino acids are considered conditionally essential, meaning they can be synthesized in the human body, but under certain physiological conditions such as illness or stress, the body's demand for them may exceed its capacity to produce them.

Food business operators (FBOs) add amino acids and their derivatives to foods for nutritional purposes. These include:

- Supporting individuals who cannot consume intact proteins (e.g., due to metabolic or digestive disorders)
- Supplementing products that contain incomplete protein sources
- Fortifying products to restore amino acid content lost during manufacturing or handling

Several regulatory authorities have established detailed, country-specific rules governing the addition of amino acids for nutritional or other non-technological purposes. These typically define permitted forms of amino acids (e.g., free acids, salts) and set purity standards for each substance.

However, these regulations can vary significantly between jurisdictions. In practice, this variability may:

- Impede the free movement of foods containing added amino acids, including FSDU.
- Complicate efforts to align quality requirements for amino acids and their use
- Create unequal conditions of competition, ultimately affecting the functioning of international trade

To address these challenges, International Special Dietary Foods Industries (ISDI) has worked to clarify and identify amino acids and their associated forms which have a history of safe use in nutritional products and for which appropriate purity standards are available.

The Codex Alimentarius provides a collection of internationally recognized foods standards. While there are no stand-alone Codex texts dedicated solely to amino acids, several standards and guidelines include provisions for their safe and nutritionally appropriate use in specific food categories, particularly FSDU.

One foundational document is the General Principles for the Addition of Essential Nutrients to Foods (CAC/GL 9-1987). This guideline outlines principles for the safe addition of essential nutrients, including amino acids, to foods. It emphasizes that nutrient addition should serve a defined purpose, such as correcting deficiencies or supporting health maintenance by helping achieve recommended intake levels. Several other Codex standards and guidelines establish provisions for the safe and nutritionally appropriate use of amino acids in FSDU such as:

CXS 72-1981	Standard for Infant Formula and Formulas for Special Medical Purposes Intended for Infants
CXS 156-1987	Standard for Follow-Up Formula for Older Infants and Product for Young Children
CXG 10-1979	Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses Intended for Infants and Young Children
CXG 8-1991	Guidelines on Formulated Supplementary Foods for Older Infants and Young Children
CXS 74-1981	Standard for Processed Cereal-Based Foods for Infants and Young Children
CXG 95-2022	Guidelines for Ready-to-Use Therapeutic Foods
CXS 181-1991	Standard for Formula Foods for Use in Weight-Control Diets
CXS 203-1995	Standard for Formula Foods for Use in Very Low Energy Diets for Weight Reduction

All Codex Standards and Guidelines are available on the Codex website.

Annex I provides excerpts from these Codex texts that address the use of amino acids in FSDU.

Codex Committees also play pivotal roles to support the safe addition of amino acids in foods:

- **Codex Committee on Methods of Analysis and Sampling (CCMAS)**: Endorses methods for analysing amino acids in foods, such as methods for total amino acids and tryptophan in FSDU and infant formula. (CXS 234-1999)
- **Codex Committee on Food Additives (CCFA)**: Evaluates and sets provisions for the safe use of food additives, including amino acids used as additives for non-nutritional purposes, ensuring they meet safety standards and are used appropriately in food products.
- **Codex Committee on Food Labelling (CCFL)**: Develops guidelines for labelling foods. Proper labelling ensures consumers are informed about the presence of amino acids in their food.

In addition to Codex, national competent authorities—such as the China National Health Commission (NHC), the European Union, Food Standards Australia New Zealand (FSANZ), and the US Food and Drug Administration (FDA)—have established regulatory frameworks governing the addition of amino acids in specific foods. These various regulations are consolidated in the ISDI document "Annex II: Summary of purity requirements and permitted amino acids for use in FSDU according to national regulations", which compiles the relevant requirements from major exporting and importing markets, including the EU, US, China, Australia, and New Zealand.

KEY CONCEPTS IN COMPOSING THE TABLE OF AMINO ACIDS AND THEIR DERIVATIVES

The proposed listing of amino acids and derivatives for food use 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 formulations including FSDU formulation.

I. FORMS OF AMINO ACIDS

Amino acids exhibit a high degree of structural flexibility because of their conformational freedom and chemical versatility because they can act as both bases and acids. Therefore, various forms of amino acids exist in nature or are produced through fermentation, enzymatic or chemical methods. 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, NH4+, as well as HCl forms. Different forms of amino acids have diverse organoleptic properties, physical appearance and stability but not significantly different nutritional values, or metabolic pathways in the human body.

II. SPECIFICATIONS (MONOGRAPHS)

Defining appropriate purity standards and specifications for amino acids is a critical step in ensuring their safe use in human nutrition. All FBOs, including suppliers of amino acids for food use and manufacturers of finished products, are responsible for ensuring product safety.

When added for nutritional purposes, Codex Alimentarius only stipulates purity requirements for amino acids when they are used in FSDU intended for infants and young children. As outlined in the Advisory Lists of Nutrient Compounds for Use in Foods for Special Dietary Uses intended for Infants and Young Children (CAC/GL 10-1979) the acceptable guideline references and internationally recognized compendia (e.g., FCC, USP, EP, etc.) are provided for each permitted amino acid. It should also be noted that certain amino acids (e.g., glutamates, INS 621–625) are permitted as food additives when used for technological purposes. In such cases, Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established appropriate specifications under their intended use as additives.

While CAC/GL 10-1979 provides guidance on purity specifications for amino acids used in FSDU intended for infants and young children, it does not cover amino acids added to other food categories, including FSDU for older children and adults.

In the absence of Codex-defined specifications for these broader applications, FBOs must ensure that amino acids used in such products meet appropriate standards of identity, purity, and quality. This includes:

- Selecting specifications from internationally recognized compendia such as the Food Chemicals Codex (FCC), United States Pharmacopeia (USP), or European Pharmacopoeia (EP),
- Ensuring that the selected specification is fit for purpose, based on the intended use, target population, and food matrix, and
- Verifying that the ingredient complies with national or regional regulations, when applicable.

Ultimately, it is the responsibility of the ingredient supplier and the finished product manufacturer to ensure that the amino acid meets the necessary quality standards and is suitable for its intended nutritional function.

III. OTHER SPECIFICATIONS (MONOGRAPHS)

Because free amino acids have technological properties and taste, some of them are authorized as food additives, notably L-glutamic acid and L-glutamates (INS 620-625), glycine (INS 640), L-leucin (INS 641), L-cysteine (INS 920). For these substances, when used as food additives, JECFA has already determined appropriate specifications (CXS 192-1995). However, the food additive specifications apply on use of the substance for one or more of the technological functions applicable to food additives; limited food categories; and use only in quantities necessary to achieve the required technological effects. While those specifications apply legally to amino acids used as additives, 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.

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 laws 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 sourcing ingredients, including amino acids and derivatives, only from manufacturers using HACCP-based food safety procedures and following current Good Manufacturing Practice (GMP).

NON-EXHAUSTIVE LIST OF AMINO ACIDS/DERIVATIVES

IDENTITY AND PURITY SPECIFICATIONS

Amino Acids[1]	European Pharmacopeia (EP)	Food Chemical Codex (FCC)	US Pharmacopeia (USP)	Other
L-alanine	✓	✓	✓	
L-arginine	✓	✓	✓	
L-asparagine		✓	✓	
L-aspartic acid	✓	✓	✓	
L-citrulline		✓	✓	
L-cysteine		✓		INS 920
L-cystine	✓	✓	✓	
L-histidine	✓	✓	✓	
L-glutamic acid	✓	✓	✓	INS 620-625
L-glutamine		✓	✓	
glycine	✓	✓	✓	INS 640
L-isoleucine	✓	✓	✓	
L-leucine	✓	✓	✓	INS 641
L-lysine	✓	✓		
L-methionine	✓	✓	✓	
L-phenylalanine	✓	✓	✓	
L-proline	✓	✓	✓	
L-serine	✓	✓	✓	
L-threonine	✓	✓	✓	
L-tryptophan	✓	✓	✓	
L-tyrosine	✓	✓	✓	
L-valine	✓	✓	✓	
D,L-methionine		✓		

[1] 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

Derivatives	European Pharmacopeia (EP)	Food Chemical Codex (FCC)	US Pharmacopeia (USP)	Other
N-acetyl-L-methionine		✓	✓	
L-carnitine		✓	✓	
Taurine		✓	✓	
L-lysine acetate	✓		✓	
Creatine		✓	✓	

METHODS OF ANALYSIS

1. Protein Quantity

a. Total Nitrogen (Kjeldahl and Dumas)

i. Kjeldahl – ISO 8968-1| IDF 20-1 or equivalent

ii. Dumas – ISO 14891:2002 | IDF 185:2002 or equivalent

b. Amino acid analysis - AOAC 2018.06| ISO 4214|IDF 254| AACC 07-50.01 and AOAC 2017.03 or equivalent

Comparison of analytical methods for protein quantity

	Principle	Regulatory use	Drawbacks
Total Nitrogen by Kjeldahl- ISO 8968-1 | IDF 20-1 or equivalent	Method for the determination of the nitrogen content and crude protein calculation of milk and milk products by the Kjeldahl principle, using traditional and block digestion methods.	Applicable to liquid cow's (whole, partially skimmed or skimmed milk), goat's and sheep's whole milk; hard, semi-hard and processed cheese; dried milk and dried milk products (including milk-based infant formulae, milk protein concentrate, whey protein concentrate, casein and caseinate). Not applicable to samples containing ammonium caseinate.	Susceptible to economic adulteration with highly nitrogenous organic compounds (i.e., melamine).
Total Nitrogen by Dumas- ISO 14891:2002 | IDF 185:2002 or equivalent	Method using combustion according to the Dumas principle.	Total nitrogen content of milk and milk products.	Same as Kjeldahl above, as well as having less specificity. Resultantly it may also pick up inorganic nitrogen (i.e., nitrates and nitrites).
Amino acid analysis- AOAC 2018.06 | ISO 4214 | IDF 254 | AACC 07-50.01 and AOAC 2017.03 or equivalent	▪ AOAC 2018.06/ISO 4214:2022/ AACC 07-50.01 - method for quantitative determination of total amino acids using ACQ derivatization followed by UHPLC separation and UV detection. Method determines, in one analysis, the following amino acids: alanine, arginine, aspartic acid (combined with asparagine), cystine (dimer of cysteine, combined with cysteine), glutamic acid (combined with glutamine), glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tyrosine, and valine. ▪ AOAC 2017.03 – method for quantitative determination of tryptophan using HPLC separation and FL detection.	Methods are applicable to infant and adult/paediatric nutritional formulas, dairy products and other matrices such as cereals. It was validated in infant formulas (milk- and soy-based, including partially hydrolysed and elemental products), toddler formula, adult nutritional powder, UHT skimmed milk, whey powder, sodium caseinate, whole milk powder, bran, pet food, dry pet food, and breakfast cereal	Analysis of full amino acid profile requires testing with two methods. Information on glutamine/glutamic acid and asparagine/aspartic acid ratios are lost.

2. Protein Qualtity (and digestibility)

Protein quality refers to the ability of dietary protein to meet the body's essential amino acid requirements and support growth and maintenance. Evaluating protein quality is especially critical in products like infant formulas, where regulatory bodies require evidence of sufficient biological value. Several methods exist to assess protein quality, each with distinct principles and limitations.

Comparison of analytical methods for protein quaLtity

	Principle	Regulatory use	Drawbacks
Protein Efficiency Ratio (PER)- AOAC 960.48 or equivalent	Measures weight gain in rats over 28 days relative to protein intake. Compared to a casein control diet.	▪ Required by the U.S. FDA for infant formula protein quality assessment. ▪ Cited in 21 CFR §106.96(f) via AOAC Method 960.48.	▪ Does not assess amino acid profile. ▪ Antinutritional factors cannot be characterized. ▪ Differences in PER values are not proportional ▪ Interlaboratory variability. ▪ Weight gain does not reflect tissue maintenance. ▪ Rat growth differs from human growth.

	Principle	Regulatory use	Drawbacks
Protein Digestibility Corrected Amino Acid Score (PDCAAS)	Evaluates protein quality by comparing the amount of the first limiting essential amino acid in the test protein to its amount in an ideal reference pattern. This ratio is then corrected for bioavailability using a 9-day rat faecal digestibility test (human balance studies should be preferred when available), which estimates crude protein digestibility based on the difference between nitrogen intake and nitrogen excreted in faeces.	The Joint FAO/WHO Expert Consultation on Protein Quality Evaluation (FAO/WHO, 1991) recommended the PDCAAS as the preferred method for assessing protein quality in human nutrition.	▪ PDCAAS values are truncated to 1 at most ▪ Scoring patterns do not include conditionally indispensable amino acids ▪ Faecal nitrogen takes microbiota metabolism into account making the nitrogen balance inaccurate. ▪ Quality is driven by the limiting amino acid, but bioavailability is determined for the whole protein ▪ Overestimates protein quality of products containing antinutritional factors
Digestible Indispensable Amino Acid Score (DIAAS) - ISO/DIS 24167 | IDF 261[2]	Evaluates protein quality by multiplying the content of each amino acid by its true ileal digestibility and comparing this corrected value to the ideal reference pattern. The true ileal digestibility should preferably be determined in humans but if this is not possible, in growing pigs or in growing rats in that order. Digestibility is calculated by comparing the amino acid content of the diet with that in the terminal ileal digesta.	The FAO expert consultation on dietary protein quality evaluation in human nutrition (FAO, 2013) recommended DIAAS as the preferred method in assessing protein quality in human nutrition, while acknowledging that, in the absence of true ileal digestibility data, PDCAAS remains the method of choice.	▪ Ileal amino acid digestibility dataset is insufficient. Requires more data (humans vs animals) ▪ Considers only antinutritional factors that directly affect digestion ▪ Limited data for processed foods ▪ No official AOAC method for analysis of individual amino acids in in-vitro digestion samples yet ▪ Scoring pattern does not include conditionally indispensable amino acids

[2] At the time of finalizing this brochure, the method was under final stage of standardization, which is expected to be completed by February 2026. This method has not yet been validated for use in FSDU matrices, but remains the best available approach at present.

ANNEX I

Compilation of relevant texts in Codex standards on the addition of amino acids in foods

Codex Standards / Guidelines	Relevant texts in Codex Standards / Guidelines
Standard for infant formula and formulas for special medical purposes intended for infants (CXS 72-1981)	**SECTION A: STANDARD FOR INFANT FORMULA, footnote 2 and 3 as follows:** 2) For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breastmilk as defined in Annex I); nevertheless, for calculation purposes, the concentrations of tyrosine and phenylalanine may be added together. The concentrations of methionine and cysteine may be added together if the ratio is less than 2:1; in the case that the ratio is between 2:1 and 3:1 the suitability of the formula must be demonstrated by clinical testing. 3) Isolated amino acids may be added to Infant Formula only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms of amino acids shall be used. Annex I on Essential and semi essential amino acids in breast milk
Standard for follow-up formula for older infant and product for young children (CXS 156-1987)	**Section 3 ESSENTIAL COMPOSITION AND QUALITY FACTORS, Clause 3.1.3 (a), footnote 3:** Isolated amino acids may be added to follow-up formula for older infants only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms of amino acids shall be used.
Advisory list of nutrient compounds for use in foods for special dietary uses intended for infant and young children (CXG 10-1979)	**Table C: ADVISORY LIST OF AMINO ACIDS AND OTHER NUTRIENTS FOR USE IN FOODS FOR SPECIAL DIETARY USES INTENDED FOR INFANTS AND YOUNG CHILDREN** See Annex I
Guidelines on formulated complementary foods for older infants and young children (CXG 8-1991)	**Section 6 NUTRITIONAL COMPOSITION AND QUALITY FACTORS:** Clause 6.3.2 The Protein Digestibility Corrected Amino Acid Score (PDCAAS)8910 should not be less than 70 per cent of that of the WHO amino acid reference pattern for children from 2 – 5 years. Clause 6.3.3 If, for technical reasons, the PDCAAS digestibility of a protein cannot be determined, the protein quality should be measured by biological assays. Alternatively, the protein quality may be calculated from published data on essential amino acid patterns of dietary proteins and their digestibility. Clause 6.3.4 The addition of methionine, lysine, tryptophan or other limiting amino acids, solely in the L-form should be contemplated only when, for economic and technological reasons, no mixture of vegetable and/or animal proteins makes it possible to obtain an adequate protein quality (see 6.3.2).
Standard for processed cereal-based foods for infants and young children (CXS 74-1981)	**Section 3 ESSENTIAL COMPOSITION AND QUALITY FACTORS, clause 3.3.1:** In all cases, the addition of amino acids is permitted solely for the purpose of improving the nutritional value of the protein mixture, and only in the proportions necessary for that purpose. Only natural forms of L-amino acids should be used.

Codex Standards / Guidelines	Relevant texts in Codex Standards / Guidelines
Guidelines for ready-to-use therapeutic foods (CXG 95-2022)	**Section 6 NUTRITIONAL COMPOSITION AND QUALITY FACTORS, clause 6.2:** Protein should provide 10 percent to 12 percent of the total energy. Protein quality should be determined using protein digestibility corrected amino acid score (PDCAAS), calculated according to the reference amino acid requirement and scoring patterns related to catch-up growth of 10 g/kg per day in the target population for RUTF which is children with SAM aged from 6 to 59 months. For all RUTF formulations, the PDCAAS shall not be less than 0.9. The PDCAAS shall be calculated using appropriate digestibility values and the reference amino acid pattern as stipulated in the Report of the FAO Expert Working Group: Protein quality assessment in follow-up formula for young children and ready-to-use therapeutic foods (2018). High quality protein will be achieved with RUTF formulations containing a minimum of 50 percent of protein from milk products. In formulations with lower PDCAAS scores, the quality and/or quantity of protein should be adjusted to achieve the desired value. The addition of limiting amino acids, solely in the L-form, shall be permitted only in amounts necessary to improve the protein quality of the RUTF.
Standard for formula foods for use in weight- control diets (CXS 181-1991)	**Section 3 ESSENTIAL COMPOSITION AND QUALITY FACTORS, clause 3.2.1.3:** Essential amino acids may be added to improve protein quality only in amounts necessary for this purpose. Only L-forms of amino acids shall be used, except that DL-methionine may be used
Standard for formula foods for use in very low energy diets for weight reduction (CXS 203-1995)	**Section 3 ESSENTIAL COMPOSITION AND QUALITY FACTORS, clause 3.2.1:** ▪ Not less than 50 g protein with a nutritional quality equivalent to a protein-digestibility-corrected amino acid score of 1 shall be present in the recommended daily intake of energy. ▪ Essential amino acids may be added to improve protein quality only in amounts necessary for this purpose. Only L-forms of amino acids shall be used, except that DL-methionine may be used.

NOTES

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