

Title 21—Food and Drugs

CHAPTER I—FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER B—FOOD AND FOOD PRODUCTS

PART 121—FOOD ADDITIVES

Amino Acids in Food for Human Consumption

CONDITIONS OF SAFE USE IN FOOD AND DELETION FROM GRAS LIST

A proposal was published in the FEDERAL REGISTER of April 6, 1972 (37 FR 6938) to establish the conditions for safe use for amino acids used to improve the protein value of food, and to delete amino acids for nutritive purposes in the human diet from the GRAS list, § 121.101(d)(5) (21 CFR 121.101).

Uncontrolled uses of amino acids in the fortification of certain foods may result in risk to the public health from excessive intakes of free amino acids. Studies on experimental animals have shown that excessive intake of amino acids and amino acid imbalance can include growth retardation and degeneration of certain organs which can lead to the animals' early death. On the other hand, properly controlled additions of the amino acid(s) to appropriate protein-containing foods can benefit the consumer by improving the biological quality of the proteins.

Thirty-nine comments were received on the proposal. Twenty-eight comments were from manufacturers or associations of manufacturers that either produce amino acids or foods in which amino acids are used, or both. Nine comments were from professional scientists in health and allied fields associated with governmental or non-profit organizations, institutions, and associations. One comment was received from a medical group and one was received from a public interest group.

The principal comments raised and the Commissioners' conclusions thereon are as follows:

APPROPRIATENESS OF THE LIMITATIONS FOR USE OF AMINO ACIDS

1. A number of comments discussed the requirement that the finished food to which the amino acids are added should furnish at least 6.5 grams of intact protein per day. Many objected to this on the basis that there are a number of foods to which the addition of amino acids will produce some benefit, but which supply less than 6.5 grams of intact protein per day. Some comments stated that since the nutrition labeling proposal published in the FEDERAL REGISTER on March 30, 1972 (37 FR 6493) considered a level of 5 percent of the U.S. Recommended Daily Allowance (3.25 grams) to provide a significant contribution of nutrients for nutrition labeling purposes, this lower figure should apply to this regulation as well.

The Commissioner recognizes that the proper addition of amino acids to a food may improve the nutritional quality thereof. In order that the fortification of foods be truly significant in relation

to the diet of the United States consumer, it is concluded that amino acid fortification should be permitted for only those foods containing at least 10 percent of the U.S. Recommended Daily Allowance (U.S. RDA) of protein, which is 65 grams per day for adults, § 1.17(c)(7)(ii)(a) (21 CFR 1.17). There is no merit in the contention that a level of 5 percent should be adopted merely on the basis that such a nutrient level was proposed for the cutoff point above which nutrition labeling could be used since that level related to significance on a serving basis only and not to the daily intake. The nutrition labeling regulations require a level of 10 percent of the U.S. RDA for any claim of nutritional significance or superiority, § 1.17(c)(v).

2. Two comments requested clarification of the term "intact protein" as used in the proposal. Another suggested modification to permit supplementation of partial hydrolyzed protein.

The Commissioner concludes that revision of the wording to limit the addition of amino acids to "foods containing primarily intact naturally occurring protein" will clarify this provision. This language is adopted to eliminate the possibility of adding amino acids to foods containing no protein but to permit the fortification of foods where some of the original protein may have been hydrolyzed.

3. A number of objections were made to the requirement that the protein efficiency ratio (PER) of the food to be supplemented must be less than 2.5, i.e., less than 100 percent of the adjusted PER of casein, and to the requirement that the PER of an amino acid supplemented food in its finished form must be 2.5 or more. Other comments stated that such restrictions would prevent the addition of amino acids to improve foods containing good quality protein, even though a PER of 2.5 could not be reached. These comments also pointed out that in placing the minimum for improvement of the finished food so high, undue emphasis was placed on meat, milk, and eggs as the preferred protein sources in the diet. Arguments were also advanced that, since cereal grains are a common and good protein source in many diets, particularly in other countries, supplementation of such foods should be provided for permitting fortification to a minimum PER of 2.0 (80 percent of casein).

The Commissioner has concluded that there is no reason to permit amino acid supplementation unless it will provide for a significant improvement in the protein quality. Exceptions to the PER limitation of 100 percent of casein will be considered separately on a case by case basis upon receipt of a petition therefor, providing that the minimum level requested is not less than 80 percent of casein.

It is also concluded that there is no reason to restrict fortification of a food already containing an original PER of 2.5 or more, if such fortification will provide a significant increase ((P) value of less than 0.05) in the original PER.

Since the PER test is a biological value test, a statistically significant improvement in the protein quality will provide a nutritionally significant improvement.

4. Other objections raised the issue that the requirement of a PER increase of 0.25 for each added amino acid is too severe and should be dropped. Some did not quarrel with the 0.25 requirement but pointed out that two or more amino acids may be needed in combination to attain the 0.25 increase. One comment suggested that it would be preferable to measure the value of any addition of amino acid(s) by determining if the resultant PER showed an increase over the PER of the naturally occurring intact protein by an amount statistically significant with a probability (P) value of less than 0.05.

The Commissioner recognizes the need to prevent random addition of amino acids to food. He also recognizes the fact that, in some protein sources, there may be more than one limiting amino acid needed in combination to produce a significant increase in the PER. Accordingly, the Commissioner has concluded to retain the requirement that a significant increase in PER be reached if any addition of amino acids is made. He also concludes that a combination of two or more amino acids should be permitted to achieve the significant increase if a lesser number of amino acids cannot produce the required increase. A statistically significant increase in the PER, which will provide a nutritionally significant improvement in the protein, should be required rather than a single numerical value since there may be situations when an increase of 0.25 PER by adding a limiting amino acid(s) may not be statistically significant at a (P) value of less than .05. A significant increase in the PER will aid in producing a significant source of protein contribution to the diet.

ADEQUACY OF THE METHOD FOR MEASURING PER

Some comments questioned the use of casein as the reference standard and the use of the PER test for protein evaluation. One comment asked for clarification that the test is run isonitrogenously.

The use of casein as a reference standard in determining the PER of protein is in accordance with the method described in sections 39.166-39.170, "Official Methods of Analysis of the Association of Official Analytical Chemists," 11th Edition, 1970. The method requires that the test be run isonitrogenously. A uniform supply of casein can be obtained, whereas a uniform source of other purified proteins such as lactalbumin and whole egg is not readily available. Casein has an acceptable essential amino acid pattern. The limitations of the PER test are recognized, but at this time it is the best method available and the

¹ Copies may be obtained from: Association of Official Analytical Chemists P. O. Box 640, Benjamin Franklin Station Washington, D. C. 20044.

official method for regulatory purposes. It is pertinent to recognize that many of the protein foods or protein supplemented foods will be used by children and it is therefore appropriate to use an assay which employs a growing animal as the test subject. Accordingly, the Commissioner concludes that the method provided is an appropriate one at this time.

LIMITATION OF THE AMINO ACID ADDITION FOR NUTRITIVE USE ONLY

A number of manufacturers took issue with limiting the use of amino acids for nutritive purposes on the basis that use of amino acids for other purposes would no longer be permitted.

No action is being taken at this time to remove from GRAS classification other amino acids or their derivatives that have other than nutritive uses. Section 121.101(d)(5) has provided authority only for using the ingredients listed thereunder as nutrients and not for other uses. If amino acids are used for technological uses not covered in the published GRAS list or in other regulations it is possible to request concurrence therefor by submission of a petition to the Food and Drug Administration for GRAS affirmation pursuant to § 121.40.

LIMITATION OF ACCEPTABLE ISOMERS TO THE L-FORM OF AMINO ACIDS

There were contrasting views expressed on the use of the various isomeric forms (the natural L-form or the commercially available mixtures of DL-forms) of amino acids. Some felt that more consideration should be given to whether only L-isomers are acceptable, offering references to certain scientific studies purporting to show some usefulness of the DL-form. Others suggested that only L-isomers should be used until further studies are carried out on the effect of the DL-isomers on man.

Because of the substantial lack of information on the biological effectiveness and safety of the DL-isomers, the Commissioner concludes that the acceptable forms of the amino acids should be restricted to the L-form except for DL-methionine and for glycine. There is appreciably more understanding of the safety of DL-methionine added to foods than there is for the DL-forms of the other amino acids. DL-methionine has been investigated and found to be acceptable as long as it is not used in infant food. D-methionine ingestion by infants may lead to a methioninuria that may hinder the proper diagnosis of a disease condition. Although adults and children also exhibit methioninuria following D-methionine ingestion, the diagnostic significance of the amino acid in the urine is of much less relative importance. Glycine does not occur in an optically active form.

Petitions may be submitted to establish the safety and nutritional value of commercially available mixtures of DL-forms when the required supporting data become available.

ACCEPTABILITY OF ADDITIONAL FORMS OF AMINO ACIDS

A number of comments pointed out the safety and usefulness of the sodium and potassium salts and acetate and sulfate forms of the amino acids and L-asparagine and L-glutamine.

The Commissioner concludes that except for the acetate and sulfate forms, these are appropriate and are included in the final order. The acetate and sulfate forms have no history of safe use and may not be used prior to promulgation of a food additive regulation.

USE OF AMINO ACIDS IN FORMULATIONS OF SPECIAL FOODS FOR NUTRITIONAL USE IN MEDICAL CONDITIONS

Several comments raised the question whether the regulation should cover amino acids used in special foods for controlled diets.

Such foods are intended for use solely under medical supervision to meet nutritional requirements in specific medical conditions. The quality and usefulness of these products must be determined on an individual product basis because of special nutritional needs dictated by the pathophysiologic conditions of a particular patient. The amino acids used in such products must be safe and of food grade, but it is inappropriate that the limitations relating to the amino acid fortification of protein in regular diets apply to them. Accordingly, the Commissioner exempts these foods for special dietary use from certain provisions of the regulation set forth below. Such foods shall be subject to all of the applicable requirements of 21 CFR Part 125.

AMINO ACID CONTENT OF EGG PROTEIN AS BASIS FOR MAXIMUM USE LEVELS

Some comments claimed that the upper limit of amino acid addition should be based only upon the amount demonstrated to achieve the maximum PER value for a food protein.

The Commissioner concludes that it is in the best interest of the consumer to permit and encourage rational fortification of foods with amino acids by limiting permissible supplementation to a safe level. A standard protein with established safety was needed to establish such limits, preferably one with high biological quality. Egg protein has the highest biological quality of any naturally occurring protein. It is generally agreed that the relative amino acid composition of egg is an ideal pattern for nutritional value and the proportion of individual essential amino acids to total protein content is generally the highest of most protein-containing foods in common use.

ILLEGALITY OF THE PROPOSED REGULATION

A public interest group alleged that the proposed regulation is illegal on the ground that it does not comply with section 409 of the act.

The Commissioner concludes that promulgation of this regulation is in accord with his broad general responsibility for protection of the public health, and is specifically in accord with section 409 of

the act and § 121.41 of the food additive regulations. This regulation is issued on the Commissioner's initiative pursuant to section 409(d) of the act. The Commissioner has concluded, on the basis of all of the scientific literature and other available information, that the amino acids have been shown by all appropriate methods to be safe under the conditions of use established in this regulation.

USE OF AMINO ACIDS FOR ANIMALS

Two firms raised questions about the status of amino acids used in animal feed if the proposed deletion from the GRAS list were accomplished.

Recognizing that amino acids are used in animal feeds and considering that the action taken herein is concerned with uses of amino acids in human food, the Commissioner concludes that the presently listed amino acids may remain on the existing GRAS list for animal feed until such time as a separate GRAS list for animal food ingredients is issued.

VARIATIONS IN ASSAY RESULTS

One comment suggested that a 10 percent excess over the allowable maximum amounts of individual amino acids should be permitted because of the variability in the assay methods available.

The Commissioner has considered the suggestion carefully and has concluded that there is no merit in providing for a 10 percent overage in the regulation. Any enforcement action that might be taken based on the maximum amounts of amino acids present would of necessity consider the variability of the method by which the amounts were determined.

LISTING OF ESSENTIAL AND NON-ESSENTIAL AMINO ACIDS

Several comments questioned the listing of nonessential amino acids with essential amino acids since the non-essential amino acids are usually thought not to improve the protein efficiency ratio.

The Commissioner recognizes that the addition of nonessential amino acids is unlikely to alter the PER. However, the total intake of non-specific nitrogen found in nonessential amino acids not only may have a sparing effect and thus influence the requirements of the essential amino acids, but also may provide properties important for foods used solely under medical supervision to meet nutritional requirements in specific medical conditions. Accordingly, the Commissioner concludes that it is inappropriate to separate the two classes of amino acids within the context of the regulation.

SPECIFICATIONS FOR AMINO ACIDS

Comments were received that certain amino acid specifications in both the Food Chemicals Codex and in NAS-NRC Publication No. 1344, referenced in the proposal are inappropriate.

Specifications in the latest edition of the Food Chemicals Codex are regarded by the Commissioner as the food grade specifications for food additives unless specifically stated to be otherwise in any given food additive regulation. Comments regarding a need for changes or

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Inclusions in these specifications should be addressed to the Codex. Specifications in NAS-NRC Publication No. 1344 are retained for the four amino acids not yet included in the Codex.

GENERAL

One scientist opposed the entire concept of amino acid fortification and stated that improvement of protein quality by fortification with free amino acids may create an imbalanced diet and undesirable effects on human physiology. The new regulation is designed to prevent such a situation by limiting the amounts, isomers, and combinations permitted, based upon the scientific evidence and the considered judgment of nutritional scientists.

The public interest group requested that the data necessary to demonstrate compliance with paragraph (d) of the regulation should be submitted to the Food and Drug Administration so that the public would be able to review it. The

Commissioner concludes that, like other quality control records, it is sufficient that this data be retained at the company and available for inspection by the Food and Drug Administration. It would be impracticable and burdensome for every food manufacturer using amino acids to submit such data to the Food and Drug Administration.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1785-1788; 21 U.S.C. 321(s), 348, 371(a)) and under the authority delegated to the Commissioner (21 CFR 2.120), Part 121 is amended as follows:

§ 121.101 [Amended]

1. In subparagraph (5) of § 121.101(d) in the "Limitations, restrictions or explanations" column by adding the text "Food additive regulation § 121.1002" for the following amino acids:

- L-Alanine
- L-Arginine
- L-Arginine Monohydrochloride
- L-Cysteine Monohydrochloride
- L-Cystine
- Glycine
- L-Leucine
- DL-Methionine
- L-Methionine
- L-Tryptophan
- L-Phenylalanine
- L-Proline
- L-Serine
- L-Threonine
- Glutamic Acid Hydrochloride
- L-Isoleucine
- L-Lysine Monohydrochloride
- Monopotassium L-glutamate
- L-Tyrosine
- L-Valine

(2) As found in "Specifications and Criteria for Biochemical Compounds," NAS-NRC Publication, 3rd Edition (1972)* for the following:

- L-Asparagine
- L-Aspartic acid
- L-Glutamine
- L-Histidine

(c) The additive(s) is used or intended for use to significantly improve the biological quality of the total protein in a food containing naturally occurring primarily-intact protein that is considered a significant dietary protein source, provided that:

(1) A reasonable daily adult intake of the finished food furnishes at least 6.5 grams of naturally occurring primarily intact protein (based upon 10 percent of the daily allowance for the "reference" adult male recommended by the National Academy of Sciences in "Recommended Dietary Allowances," NAS Publication No. 1694, 7th Edition (1968)).⁴

(2) The additive(s) results in a protein efficiency ratio (PER) of protein in the finished ready-to-eat food equivalent to casein as determined by the method specified in paragraph (d) of this section.

(3) Each amino acid (or combination of the minimum number necessary to achieve a statistically significant increase) added results in a statistically significant increase in the PER as determined by the method described in paragraph (d) of this section. The minimum amount of the amino acid(s) to achieve the desired effect must be used and the increase in PER over the primarily-intact naturally occurring protein in the food must be substantiated as a statistically significant difference with at least a probability (P) value of less than 0.05.

(4) The amount of the additive added for nutritive purposes plus the amount naturally present in free and combined (as protein) form does not exceed the following levels of amino acids expressed as percent by weight of the total protein of the finished food:

* Copies may be obtained from: National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, D.C. 20037.

⁴ National Academy of Sciences, 2101 Constitution Avenue, N.W., Washington, D.C. 20037.

Product	Tolerance	Limitations, restrictions or explanations
(5) NUTRIENTS AND/OR DIETARY SUPPLEMENTS ¹		
Alanine (L- and DL-forms)	Food additive regulation § 121.1002.
Arginine (L- and DL-forms)	Do.
Aspartic acid (L- and DL-forms)	Food additive regulation § 121.1002.
Cystine (L-forms)	Food additive regulation § 121.1002.
Cystine (L- and DL-forms)	Do.
Histidine (L- and DL-forms)	Food additive regulation § 121.1002.
Isoleucine (L- and DL-forms)	Food additive regulation § 121.1002.
Leucine (L- and DL-forms)	Do.
Lysine (L- and DL-forms)	Food additive regulation § 121.1002.
Phenylalanine (L- and DL-forms)	Food additive regulation § 121.1002.
Proline (L- and DL-forms)	Food additive regulation § 121.1002.
Serine (L- and DL-forms)	Food additive regulation § 121.1002.
Threonine (L- and DL-forms)	Food additive regulation § 121.1002.
Tryptophane (L- and DL-forms)	Food additive regulation § 121.1002.
Tyrosine (L- and DL-forms)	Do.
Valine (L- and DL-forms)	Do.

¹ Amino acids listed may be free, hydrochloride salt, hydrated, or anhydrous form, where applicable.

2. By adding a new section to Subpart D, to read as follows:

§ 121.1002 Amino acids.

The food additive amino acids may be safely used as nutrients added to foods in accordance with the following conditions:

(a) The food additive consists of one or more of the following individual amino acids in the free, hydrated or anhydrous form or as the hydrochloride, sodium or potassium salts:

- L-Alanine
- L-Arginine
- L-Asparagine
- L-Aspartic acid
- L-Cysteine
- L-Cystine
- L-Glutamic acid
- L-Glutamine
- Glycine

- L-Histidine
- L-Isoleucine
- L-Leucine
- L-Lysine
- DL-Methionine (not for infant foods)
- L-Methionine
- L-Phenylalanine
- L-Proline
- L-Serine
- L-Threonine
- L-Tryptophan
- L-Tyrosine
- L-Valine

(b) The food additive meets the following specifications:

(1) As found in "Food Chemicals Codex," National Academy of Sciences-National Research Council (NAS-NRC), 2nd Edition (1972)³ for the following:

³ Copies may be obtained from: National Academy of Sciences 2101 Constitution Avenue, N.W. Washington, D.C. 20037

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	Percent by weight of total protein (expressed as free amino acid)
L-Alanine	6.1
L-Arginine	6.6
L-Aspartic acid (including L-asparagine)	7.0
L-Cystine (including L-cysteine)	2.3
L-Glutamic acid (including L-glutamine)	12.4
Glycine	3.5
L-Histidine	2.4
L-Isoleucine	6.6
L-Leucine	8.8
L-Lysine	6.4
L- and DL-Methionine	3.1
L-Phenylalanine	5.8
L-Proline	4.2
L-Serine	3.4
L-Threonine	5.0
L-Tryptophan	1.6
L-Tyrosine	4.3
L-Valine	7.4

(d) Compliance with the limitations concerning PER under paragraph (c) of this section shall be determined by the method described in sections 39.166-39.170, "Official Methods of Analysis of the Association of Official Analytical Chemists," 11th Edition, (1970). Each manufacturer or person employing the additive(s) under the provisions of this section shall keep and maintain throughout the period of his use of the additive(s) and for a minimum of 3 years thereafter, records of the tests required by this paragraph and other records re-

quired to assure effectiveness and compliance with this regulation and shall make such records available upon request at all reasonable hours by any officer or employee of the Food and Drug Administration, or any other officer or employee acting on behalf of the Secretary of Health, Education, and Welfare and shall permit such officer or employee to conduct such inventories of raw and finished materials on hand as he deems necessary and otherwise to check the correctness of such records.

(e) To assure safe use of the additive, the label and labeling of the additive and any premix thereof shall bear, in addition to the other information required by the act, the following:

(1) The name of the amino acid(s) contained therein including the specific optical and chemical form.

(2) The amounts of each amino acid contained in any mixture.

(3) Adequate directions for use to provide a finished food meeting the limitations prescribed by paragraph (c) of this section.

(f) The food additive amino acids added as nutrients to special dietary foods that are intended for use solely under medical supervision to meet nutritional requirements in specific medical conditions and comply with the requirements of Part 125 of this chapter are exempt from the limitations in paragraphs (c) and (d) of this section and may be used in such foods at levels not to exceed good manufacturing practices.

Any person who will be adversely affected by the foregoing order may at any time on or before August 27, 1973, file with the Hearing Clerk, Food and Drug Administration, Rm. 6-83, 5600 Fishers Lane, Rockville, MD 20852, written objections thereto. Objections shall show wherein the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. If a hearing is requested, the objections shall state the issues for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Objections may be accompanied by a memorandum or brief in support thereof. Six copies of all documents shall be filed. Received objections may be seen in the above office during working hours, Monday through Friday.

Effective date. Compliance with this order may begin immediately. This order shall be effective on January 23, 1974.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1785-1788; 21 U.S.C. 321(a), 348, 371 (a)).

Dated: July 19, 1973.

A. M. SCHMIDT,
Commissioner of Food and Drugs.

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