Amino Acids

Crops

Identification

Chemical Names
The model used to illustrate amino acids used in crop production is glycine, or aminoacetic acid.

CAS Numbers:
Glycine: 56-40-6

Other Names:
See attached list for the amino acids most often found in protein. The model amino acids for crop production is glycine.

Other Codes:
none

Recommendation

Synthetic / Non-Synthetic:	National List:	Suggested Annotation:
Synthetic (Consensus)	*Not added to the National List. (Consensus)*	*Amino acids produced by chemical synthesis, such as the Strecker process or the Bucherer-Berg process; semifermentation or enzymatic processes on synthetic precursors; or using enzymes produced by a genetically modified organism (GMO) as defined by the NOSB; extracted from GMOs; produced by fermentation on an entirely synthetic (including GMO source) media; or extracted from naturally occurring organisms by use of synthetic strong acids, strong bases, or solvents; or produced by any process not explicitly described as below as "non-synthetic" are considered synthetic. (consensus)*
Not synthetic (Consensus)	*Not added to the National List (Consensus)*	*Amino acids produced from organisms that are not genetically engineered as defined by the NOSB and extracted by extracellular, mechanical, physical, biological, and / or enzymatic processes are considered non-synthetic. (Consensus)*
No consensus	*Not added to the National List*	*Amino acids produced from naturally occurring organisms cultured on a media that contains some but not all synthetic (including GMO) ingredients; and those extracted by the use of hydrolysis or ion exchange may or may not be synthetic depending on the specific circumstances, and should be reviewed on a case-by-case basis. (Not consensus)*

Characterization

Composition:
Amino acids have an amino group or amine (NH_2) adjacent to a carboxyl (COOH) group on a carbon. Glycine is generally considered the simplest amino acid. Glycine's chemical formula is H_2NCH_2COOH.

Properties:
A total of twenty different amino acids are present in protein hydrolysates, and other less common amino acids exist naturally and have biological functions. A growing number of non-protein amino acids that do not occur in nature have been synthesized. Except for glycine, all amino acids resulting from protein hydrolysis possess rotary optical activity. Amino acids that occur in plant or animal tissues are almost always in the L- enantiomer. This stereoisomerism is due to the presence of an asymmetric carbon atom. Therefore we can conclude that only the L-enantiomer amino acids may be considered non-synthetic. The D- isomers of amino acids may be present in the cell walls of microorganisms and in polypeptides endowed with antibiotic action (actinomycin D), gramicidin and tryocidin. Chemical synthesis of amino acids usually results in the creation of a DL-enantiomer or racemic mixture. Glycine is a white, odorless, crystalline powder having a sweetish taste. Solutions are acid to litmus tests. Decomposes at 233°C. Glycine is unique among the protein amino acids in that it is symmetrical and not optically active.

How Made:
Prior to 1950, most amino acids were produced by the denaturing and hydrolysis of various protein sources (Araki and Ozeki, 1991). May be isolated from protein from various sources. These may be plant, animal, or

microorganism derived and may or may not be from organisms that are genetically engineered as defined by the NOSB.

A number of amino acids are produced by fermentation. The fermentation may take place on a culture media composed of grains, sugar, molasses, yeast, or other biological material. The culture media may also be composed of petrochemicals, such as paraffin, and synthetic nutrients such as ammonium chloride, ammonium nitrate, and potassium phosphate. Extractants used may involve the use of physical and mechanical means, such as heat or maceration, as well as chemical methods such ase petroleum solvents, ammonia, strong acids, strong bases, and / or ion exchange. In a number of cases, a synthetically produced amino acid can be biologically transformed into another amino acid by a semi-fermentation or an enzymatic process. The semifermentation process involves the metabolic interaction of a fermentation organism with a synthetic precursor. An increasing number of organisms are genetically engineered. Amino acids may also be formed by reactions catalyzed by enzymes. The substrates may be naturally occurring, but they may also be synthetic, and are often both. They may also be produced by a wide number of non-biological processes that are considered to be synthetic by the TAP (Areki and Ozeki, 1991).

Glycine is the simplest amino acid, and is used in crop production as a chelating agent for micronutrients and has been used as a nitrogen fertilizer, at least on an experimental basis. As such, it is representative of amino acids used in crop production. Practically all commercial glycine is produced by synthetic processes such as the Strecker Synthesis (Areki and Ozeki, 1991). The Strecker Synthesis involves the reaction of formaldehyde, ammonia, and hydrogen cyanide, and hydrolysis of the resulting aminonitrile. It is also produced by other synthetic processes (Areki and Ozeki, 1991).

Specific Uses:
Chelating / complexing agents for cation nutrients, plant growth regulators, substrate for microbiological products, fertilizer source of nitrogen.

Action:
Plant uptake of metal nutrients are a function of the absolute levels, relative levels to each other, soil pH, oxidative state, and solution. The amino acids found in soil organic matter help protect metal cations from harmful reactions with plants and help to regulate plant uptake (Brady, 1974). A number of synthetic compounds have been developed to mimic this natural phenomenon. When a single ligand binds to a cation, that cation is considered 'complexed.' If a metal cation is joined with an organic compound at two or more exchange sites to form a ring structure, then that structure is considered a metal chelate (Meister, 1999). Two amino acids will bind to a metal to form a chelate (Ashmead et al, 1986). Chelation makes otherwise unavailable compounds plant available under normal pH conditions (AAPFCO, 1998). Chelated nutrients are more plant available than complexed nutrients, and complexed nutrients are more plant available than uncomplexed nutrients. Other amino acids used to complex or chelate cation micronutrients include lysine, glutamic acid (Miller, 1998), cysteine, and histidine (Baker and Ammerman, 1995).

AminoethoxyVinylGlycine (AVG) is used as a plant growth regulator to slow the maturation process of pome fruit by temporarily suppressing ethylene production. Other amino acids used as plant growth regulators include L-glutamic acid and gamma amino butyric acid (GABA). These act by stimulating nutrient uptake.

All amino acids have the potential to decompose into amines that can go into solution as plant-available nitrogen. Glycine appears to be the most used as a fertilizer source.

Combinations:
The metal cations most often chelated are calcium, copper, iron, magnesium, manganese, potassium, and zinc. These are usually in sulfate or occasionally in oxide form. Many formulations will be combined with synthetic fertilizers. For example, the combination of amino acid chelated nutrients with urea enhanced nutrient uptake (Ashmead, 1986).

When used as plant growth regulators, amino acids are combined with various inert ingredients used as surfactants, dispersants, carriers, fillers, spreader-stickers, and wetting agents. Many of these are synthetic. In turn, glycine and other amino acids may be included as inert ingredients in biorational pesticide formulations as part of a culture media used to grow certain microbial products.

Various complex protein sources may be decomposed into amino acids that are then turned into available nitrogen sources. Certain commercial formulations of soil amendments and foliar feeds claim 'amino acids' on the label when they are in fact using denatured protein sources such as blood meal, fish meal, whey, soy isolate or other plant or animal by-product.

Different amino acids may serve as the base for certain pesticides. For example, glycine combined with methyl phosphonate forms the herbicide glyphosate (Meister, 1999).

Status

OFPA

May be considered non-synthetic from certain sources. Not clear if synthetic amino acids fit into any exempted category for use in plant crop production, except perhaps as chelating agents for micronutrients and inert ingredients, such as nutrients in fermentation substrates for naturally occurring microorganisms.

Regulatory

Chelating agents for micronutrients regulated by state plant food control officials (AAPFCO, 1998). Plant growth regulator use is EPA regulated under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA--7 USC 136 et seq.). GABA and L-glutamic acid are considered to be reduced risk pesticides by EPA (EPA, 1998).

Status among Certifiers

Amino acids are not restricted separately from the other generic categories in which they appear. For example, those used as chelating agents for micronutrients are regulated as micronutrients. Plant growth regulators from non-synthetic sources are often restricted.

Historic Use

The greatest and longest-standing use of amino acids in organic production has been as chelating or complexing agents for micronutrients used for documented deficiencies. Several certifiers have accepted the use of amino acids as chelating agents and plant growth regulators under the assumption that they are non-synthetic.

International

The Codex Guidelines for organic production do not mention amino acids specifically in any aspect of plant crop production. However, the Guidelines do mention trace elements and natural acids with the condition for use in both cases being "Need recognized by certification body or authority" (Joint FAO/WHO Standards Programme. 1999). IFOAM restricts trace minerals, with the restrictions the responsibility of the certifier (IFOAM, 1998). Amino acids are clearly prohibited by IFOAM if they are derived from a genetically engineered source. IFOAM standards prohibit the use of synthetic growth regulators, discourage the use of non-synthetic PGRs, and states a general principle that "[g]rowth and development should take place in a natural manner" (IFOAM, 1998).

OFPA 2119(m) Criteria

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.

As chelating agents, amino acids increase the biological availability of different metals. Chelating agents in general can enhance nutrient uptake, but may also increase the uptake of toxic metals if those are also present. If cation impurities are present in micronutrient sources (e.g. cadmium), chelation of those metals would make those contaminants more readily assimilated by plants than in less available forms.

(2) The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.

Glycine is one of the least stable amino acids, rapidly degrading into ammonia, amides, and aliphatic amines (Cheshire et al., 1990). Acute oral toxicity is 3,000 mg/kg (cat) (NIEHS, 1999). Salmonella tests for mutagenicity are negative (Haworth et al., 1983). Carcinogenicity and teratogenicity studies are not available (NIEHS, 1999).

(3) The probability of environmental contamination during manufacture, use, misuse or disposal of such substance.

Formaldehyde, ammonia, and hydrogen cyanide are used in the Strecker synthetic process to produce glycine. Formaldehyde is listed as a probable carcinogen by the National Institute for Environmental Health and Safety and the International Agency for Research on Cancer (NIEHS, 1999; IARC, 1982, IARC, 1987). It is highly flammable and is released in the air and in water in manufacturing (EPA, 1999). Acute exposure at higher concentrations may cause bronchitis, pneumonia or laryngitis (Bretherick, 1986). Exposure may also cause headache, dizziness, difficult breathing and pulmonary edema. Ammonia is generally produced by reacting atmospheric nitrogen with methane at high temperatures, a process that requires much energy.

Hydrogen cyanide is produced by further processing of methane and ammonia. Hydrogen cyanide is a gas that is highly toxic. Hydrogen cyanide has a toxicity rating of 6 and is one of the fastest acting poisons known to man (Gosselin, 1984). Exposure causes paralysis, unconsciousness, convulsions, and respiratory arrest. Death usually results from exposure at 300 ppm concentrations for a few minutes (Clayton and Clayton, 1982). Manufacture of hydrogen cyanide is a significant source of atmospheric release of cyanide (Midwest Research Institute, 1993). Ammonia is a corrosive agent. Methane is a central nervous system depressant (Gosselin, 1984).

(4) The effect of the substance on human health.

While glycine and other amino acids are nutrients for humans, they may be toxic in excess and can cause allergic reactions at low thresholds in sensitive people. Exposure to free amino acids in pure available form have been long been linked to a number of genetic disorders and food allergies. The most widely studied are those related to glutamates (Coyle and Puttfarcken, 1993). Glycine inhibits neurotransmissions (Budaveri, 1996). Elevated levels of glycine have been observed in migraine patients (D'Andrea, et al., 1991; Alam, et al., 1998). It is safer to avoid exposure to free amino acids under normal circumstances. Research is incomplete on the role free amino acids play in the human system. NIEHS recommends wearing a respirator when handling glycine (NIEHS, 1999).

(5) The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.

References to agroecosystem effects in the literature are scant and speculative. Most are based on laboratory toxicological research. Glycine has a low mammalian toxicity, and appears to stimulate rather than suppress soil microbiological activity. Chelating agents may serve to reduce the amount of synthetic micronutrients needed to effectively correct deficiencies. Long-term effects of amino acids used as plant growth regulators have not been studied because the use of those products is relatively new. Most of the research and data is from sources with proprietary interests and mainly address efficacy questions.

(6) The alternatives to using the substance in terms of practices or other available materials.

There are several alternatives that are either non-synthetic or that the NOSB has already reviewed and recommended to be added to the National List. An increase in soil organic matter and subsequent biological activity can increase the availability of soil micronutrients (Alexander, 1977). Carefully selected mined mineral sources can serve to balance cations for soils where those nutrients are not in appropriate ratios.

For chelating / complexing agents used in foliar applications: citric acid from non-GMO sources are considered non-synthetic; lignosulfonic acid and humic acid derivatives have already been recommended for addition to the National List. Other chelating agents have not been considered in the context of the NOSB's recommendations on synthetic micronutrients. For example, the NOSB may want to address the use of EDTA and glucoheptanate, either by referring them to the TAP or by demurring with explicit recognition that these substances are synthetic and prohibited. It should be noted here that EDTA synthesis shares many of the same environmental pollution problems with amino acid synthesis (Midwest Research Institute, 1993).

Alternatives to use as plant growth regulators are either labor-intensive (e.g. hand thinning and multiple picking) or require different timing of planting and harvest.

As a nitrogen fertilizer: compost, nitrogen fixing legumes, more complex protein sources such as fish.

(7) Its compatibility with a system of sustainable agriculture.

As essential biological products, amino acids are necessary to sustain agricultural production and are an inevitable part of organic farming systems. However, certain sources and applications of these materials appear to be more compatible than others; certain sources may be considered entirely incompatible. Glycine is 18.66% nitrogen in a relatively plant available form when compared with more complex protein sources. When produced from ammonia, formaldehyde, and hydrogen cyanide, it is difficult to see how it is different from other synthetic sources of soluble nitrogen, such as ammonia or urea.

Discussion

Condensed Reviewer Comments

None of the reviewers have a commercial or financial interest in glycine or any other amino acid.

Reviewer 1

Review
Since proteins are composed of amino acids, it is possible (as I have done in laboratory conditions) to hydrolyze proteins to their constituent amino acids from a combination of proteolytic enzymes (as in digestion). Glycine or any other amino acid can be separated and crystallized. This would be a natural method of amino acid production but is not cost effective as chemical synthesis.

Most all commercially available amino acids, such as glycine are synthetic. Additionally all AVG (aminoethoxyvinyl glycine) is produced synthetically and therefore should be classified synthetic.

I also feel the NOSB materials database is accurate for glycine. Generally, organic soil practices should preclude having to add chelating agents even though there is documented enhancement of nutrient uptake. For those soils where a chelating agent is required I would recommend citric acid from a non-GMO source in combination with humic acid derivatives. I see no technical reason to use synthetic glycine for any crop application. Therefore I recommend that glycine and all other synthetic amino acids used for soil/crop applications not be added to the National List of Allowed Non-organic Ingredients.

Reviewer 2
1) It appears, dependent on source and manufacturing process employed, that glycine may be derived from natural, synthetic or transgenic sources. If the material is produced via the Strecker Synthesis (which according to the information provided is the most common method for production of glycine) the material is synthetic. If it is produced via transgenic methods it should be prohibited. If it is produced from non transgenic microbial digestion or hydrolysis from plant or animal proteins it is non synthetic.

2) The information regarding properties, uses and sources appears accurate and complete.

3) The manufacture and disposal consequences indicate the production of the synthetic form of this material is too dangerous to be in compliance with the OFPA. The effect on human health appears to be minimal under normal application technologies and rates of use. The other information in the OFPA criteria appears to be accurate, although the lack of available information on agrosystem biology is troubling.

4) Non synthetic foliar feeding alternatives currently available include in vessel fermentation of micro and macronutrients utilizing humic acids, compost fermentation, and/or biological chelation through aerobic digestion of basic minerals. Additionally ligno sulfonate chelates are commonly available and effective. All of these materials work very well, although they are often not as concentrated as the amino acid chelates, thus requiring higher application rates. Sulfate forms of trace minerals are inexpensive, usually synthetic, usually very effective and as concentrated as the amino acid products.

There are no good non synthetic alternatives for use as plant growth regulators. This may be the best use for amino acids. There are numerous non synthetic sources of nitrogen including: animal and plant proteins, fish extracts, leguminous crops, nitrogen fixing organisms, manures and composts. All of these appear to have less negative environmental impacts than the synthetic production of glycine. Synthetic glycine is not compatible with the OFPA with regards to its use as a nitrogen fertilizer; it is little different from the production of urea, ammonium nitrate and other prohibited synthetic sources of nitrogen.

5) The compatibility should be addressed via consideration of the product's manufacturing process and intended use. Transgenic, Strecker and other synthetic processed forms should be prohibited. Plant, animal or non transgenic microbial extraction appear to be in compliance with the OFPA. The proposed annotation

appears appropriate and should be utilized. Amino acids should be reviewed on a case by case basis. Their use as plant growth regulators should be allowed provided the manufacturing process is in compliance. Their use as nitrogen fertilizer sources should be allowed if the manufacturing process is in compliance with the OFPA. Their use as chelating agents should be allowed if the manufacturing process is in compliance with the OFPA standards.

Reviewer 3
I believe that the NOSB should review amino acids for crop production on a case-by-case basis. There is much concern recently about the use of glutamic acid as a plant growth regulator as there are some groups that believe its use will trigger allergenic response in individuals, similar to a reaction to MSG. This is a very different issue than those covered for glycine.

Since there are other approved chelating agents recommended for inclusion on the National List, it should be a requirement that each individual amino acids' usage be approved only after demonstrating that the alternatives do not work for the same essential purpose.

I agree that a distinction needs to be made as to the process by which amino acids are produced. Only amino acids produced from naturally occurring strains of microorganisms or those derived naturally from plant or animal protein should be used on organic crops.

Conclusion

The TAP finds no basis to add any or all synthetic amino acids to the National List. The NOSB may want to review synthetic amino acids on a case-by-case basis, rather than as a class. However, based on the current use of amino acids in organic production, the addition of a single amino acid would not make much sense. While glycine may serve as a useful model, it is seldom used by itself, and instead is used with other complexing amino acids to chelate micronutrients, with other denatured protein sources as a soil amendment, or as a moiety in a larger, usually synthetic, molecule used as an herbicide or a plant growth regulator.

If the NOSB and the USDA do not add amino acids to the National List, then organic producers and certifiers will need to distinguish those amino acids that are manufactured from fossil fuels feedstocks and those that are produced by the fermentation of genetic engineered microorganisms from ones that are produced from naturally occurring strains of microorganisms, and those that are derived from plant or animal protein.

Given the concerns of those with food allergies and other sensitivities, the NOSB may want to consider adding non-synthetic amino acids to the National List of prohibited non-synthetics, either as a class or individually. While there was insufficient information for the TAP to make that recommendation, it has been raised as a concern and may merit further study if not immediate action.

The recommendation of the TAP is to take no action to add amino acids to the National List as either an allowed synthetic or as a prohibited non-synthetic, but instead to provide a clear line for the Secretary, accredited certifiers, and the organic community to be able to distinguish non-synthetic sources of amino acids that would be allowed in organic production from synthetic ones that would be prohibited.

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Amino Acids

Livestock

Identification

Chemical Names:
See the attached list for the names of protein amino acids.
Chemical names for methionine: 2-amino-4-methylthiobutyric acid; α-amino-γ-methylmercaptobutyric acid.

Other Names:
The model used to illustrate amino acids in livestock is methionine. Among the other names for methionine are DL-methionine, D-methionine, L-methionine, Met, Acimethin. See the attached table of other amino acids commonly used in food processing.

CAS Numbers:
59-51-8 (DL-methionine)
63-68-3 (L-methionine)
348-67-4 (D-methionine)

Other Codes:
International Feed Names (IFN):
DL-methionine: 5-03-86
DL-methionine hydroxy analog calcium: 5-03-87
DL-methionine hydroxy analog: 5-30-281

Recommendation

Synthetic / Non-Synthetic:	National List:	Suggested Annotation:
Synthetic (consensus--see Condensed Reviewer Comments for a discussion of synthetic v. non-synthetic amino acids)	*prohibited (2-1)*	*None. [See Condensed Reviewer Comments and Conclusions for reviewer response and possible annotations if the NOSB votes to add any or all amino acids to the recommended National List.]*

Characterization

Composition:
Amino acids have an amino group (NH_2) adjacent to a carboxyl (COOH) group on a carbon. The model amino acid for livestock production is methionine. The formula for methionine is $H_2NCH_3SCH_2CH_2COOH$.

Properties:
L-Methionine: Colorless or white lustrous plates, or a white crystalline powder. Has a slight, characteristic odor. Soluble in water, alkali solutions, and mineral acids. Slightly soluble in alcohol, insoluble in ether. MP 280-282°C. It is assymetric, forming both an L- and a D- enantiomer.

How Made:
Methionine may be isolated from naturally occurring sources, produced from genetically engineered organisms, or entirely synthesized by a wide number of processes. While methionine has been produced by fermentation in laboratory conditions, racemic mixtures of D- and L- methionine (DL-Methionine) are usually produced entirely by chemical methods (Araki and Ozeki, 1991). Methionine can be produced from the reaction of acrolein with methyl mercaptan in the presence of a catalyst (Fong, et al., 1981). Another method uses propylene, hydrogen sulfide, methane, and ammonia to make the intermediates acrolein, methylthiol, and hydrocyanic acid (DeGussa). The Strecker synthesis can be used with α-methylthiopropionaldehyde as the aldehyde (Fong, et al., 1981). A recently patented process reacts 3-methylmercaptopropionaldehyde, ammonia, hydrogen cyanide, and carbon dioxide in the presence of water in three reaction steps (Geiger et al., 1998). Other methods are discussed in the Crops Amino Acid TAP review.

Specific Uses:
The primary use of isolated amino acids in livestock production are as a feed supplement. For optimum health and performance the animal's diet must contain adequate quantities of all nutrients needed, including amino acids. The essential amino acid furthest below the level needed to build protein is known as the limiting amino acid. A shortage of the limiting amino acid will constrain animal growth, reduce feed efficiency, and in extreme cases cause a nutritional deficiency. Supplementation with isolated amino acids increases feed conversion efficiency, thus lowering feed costs per unit of weight gain or production (Pond, Church, and Pond, 1995). Methionine is often the first or second limiting amino acid in most diets, and so is most representative of amino acids fed as a nutritional supplement (Buttery and D'Mello, 1994).

Amino acids are also used in livestock health care. Methionine is used as a urine acidifier because excretion of its sulfate anion lowers urine pH. Its sulfate anion may also displace phosphate from magnesium-ammonium-phosphate hexahydrate (struvite, double phosphate, or triple phosphate if calcium is also present) crystals and uroliths, which form best at a pH above 6.4-6.6. As a result of these effects methionine is used to assist in dissolving and/or preventing uroliths, kidney stones, bladder stones or urologic syndromes thought to be caused by struvite uroliths or crystals (Lewis, Morris, and Hand, 1987). Methionine is also used to assist in the treatment and/or prevention of hepatic lipidosis because of its need for body fat mobilization and transport.

Other amino acids may be used for therapeutic purposes as well. This includes a number of non-essential protein amino acids, as well as non-protein amino acids. For example, glutamine is used in the management of enteritis because it is protective and promotes repair of injured intestines (Tremel, et al, 1994).

Action:
Amino acids form protein. Between 8 and 14 cannot be synthesized by animals and therefore must be consumed in feeding. These are considered essential (or semi-essential) for animal nutrition. Others may be produced by the animal or by organisms in the animal's gastrointestinal tract in adequate amounts. The National Academy of Sciences and most other sources on animal nutrition list arginine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine as essential (National Research Council, various years). Animals convert dietary protein into tissue protein through digestive processes. Proteins are metabolized by animals through two phases: catabolism (degradation) and anabolism (synthesis).

Combinations:
Amino acids are combined in feed rations of grains, beans, oilseeds, and other meals with antioxidants, vitamins, minerals, antibiotics, and hormones (Pond, Church, and Pond, 1995).

Status

OFPA
Amino acids do not appear on the list of synthetics that may be allowed (7 USC 6517(b)(1)(C)(i). The NOSB may want to discuss whether or not the administration of synthetic amino acids in the absence of any symptoms of illness would be considered a growth or production promoter and therefore categorically prohibited in livestock production for such purposes (7 USC 6509(c)(3)).

Regulatory
Regulated as a nutrient / dietary supplement by FDA (21 CFR 582.5475). The Association of American Feed Control Officials (AAFCO) set the standard of identity for DL-methionine as containing a minimum of 99% racemic 2-amino-4-methylthiobutyric acid (AAFCO, 1998). The AAFCO model regulation states that "the term Methionine Supplement may be used in the ingredient list on a feed tag to indicate the addition of DL-Methionine." (AAFCO, 1998.)

Status among Certifiers
A number of private certifiers prohibit the use of amino acids. Various state and private certifiers either explicitly or implicitly allow the use of essential amino acids. Their status among US certifiers remains unresolved awaiting a recommendation by the NOSB and final determination by the NOP.

Historic Use

Crystalline amino acids were generally not used as feed supplements in organic livestock production until very recently. Most current use in organic production appears to be as a supplement for laying hen feed rations.

International

The Codex guidelines do not address livestock materials at this point (Joint FAO/WHO Standards Programme. 1999). Amino acids are prohibited for use in feed by IFOAM (IFOAM, 1998). The European Standards do not include amino acids among permitted feedstuffs (European Union, 1999). Canadian standards allow essential amino acids, but explicitly prohibit ones from genetically engineered sources and state that the material may have some additional requirements. Operators are instructed to consult with their certification body for approval (Canadian General Standards Board, 1999).

OFPA 2119(m) Criteria

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems.

The primary chemical interaction is the dietary intake by animals. While many of the interactions may be regarded as beneficial, excess methionine in a diet may cause deficiencies in other amino acids and induce toxicity (D'Mello, 1994). Methionine, while often one of the most limiting amino acids, is also one that readily goes to toxic excess. Small excesses of methionine can be deleterious (Buttery and D'Mello, 1994). Excess supplemental methionine can actually depress growth and development at levels of 40 g/kg (Baker, 1989). Growth depressions resulting from excess supplemental amino acids include lesions in tissues and organs (D'Mello, 1994).

(2) The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment.

While it is nutritionally essential, methionine excesses are far more toxic to poultry than similar excesses of tryptophan, lysine, and threonine (National Research Council, 1994). Force feeding methionine to excess can result in death to chicks (National Research Council, 1994).

A dosage of 2 g / mature cat / day (20 to 30 g / kg dry diet) for 20 days induces anorexia, ataxia, cyanosis, methemoglobinemia and Heinz body formation resulting in hemolytic anemia (Maede, 1985). Rat studies of methionine is significantly toxic in excess (Regina, et al., 1993). High levels of methionine were found to be toxic to hepatic cells and liver function of the rat models. The results of this study indicated that the biochemical reason for the extreme sensitivity of mammals to excess dietary methionine is thought to be due to the accumulation of toxic catabolites, most notably, S-adenosylmethione, resulting in liver dysfunction. L-methionine has an acute LD_{50} of 4,328 mg/kg (rat) (NIEHS, 1999b). NIEHS carcinogenicity and teratogenicity are not available, but reports positive mutagenicity (NIEHS, 1999b).

Methionine is stable in crystalline form at standard temperature and pressure.

(3) The probability of environmental contamination during manufacture, use, misuse or disposal of such substance.

Synthetic production of DL-methionine involves a number of toxic source chemicals and intermediates. Each of the several manufacturing processes used to produce DL-methionine were rated as either "moderately heavy" to "extreme" (Fong, et al., 1981). Newer processes have not replaced many of the feedstocks. Several of the feedstocks are likely to result in ruptured storage tanks, leaking chemicals, and releases into the environment. The methionine production process is listed by EPA as a hazardous air pollutant (40 CFR 63.184).

Methyl mercaptan can react with water, steam, or acids to produce flammable and toxic vapors (Sax, 1984). The EPA rates methyl mercaptan fires as highly hazardous and can cause death by respiratory paralysis (EPA, 1987). Acrolein has a toxicity rating of 5 (on a scale of 1 to 6 with 6 being most toxic) (Gosselin, 1984) and it is also an aquatic herbicide (Meister, 1999). The acrolein process involves several steps that render it synthetic as well (1994). Acrolein itself is an extreme irritant.

Hydrogen cyanide is produced by further processing of methane and ammonia. Hydrogen cyanide is a gas that is highly toxic. Hydrogen cyanide has a toxicity rating of 6 and is one of the fastest acting poisons known to man (Gosselin, 1984). Exposure causes paralysis, unconsciousness, convulsions, and respiratory arrest. Death usually results from exposure at 300 ppm concentrations for a few minutes (Clayton and Clayton, 1982). Manufacture of hydrogen cyanide is a significant source of atmospheric release of cyanide (Midwest Research Institute, 1993). Ammonia is a corrosive agent. Methane is a central nervous system depressant (Gosselin, 1984).

(4) The effect of the substance on human health.

Methionine is essential in small amounts in the human diet, and is sold over-the-counter as a dietary supplement. The L- form of methionine is used extensively in human medicine for a variety of therapeutic purposes including pH and electrolyte balancing, parenteral nutrition, pharmaceutical adjuvant, and other applications. It is in fact one of the top 800 drugs in human medicine (Mosby, 1997). Methionine may cause nausea, vomiting, dizziness, and irritability and should be used with caution in patients with severe liver disease (Reynolds, 1996).

The D- form of methionine is not well utilized by humans (Lewis and Baker, 1995). Individuals may have allergic reactions to the D- isomers or a racemic mixture of DL-methionine. While a number of amino acids are considered GRAS for human consumption and as feed supplements, DL-methionine is not (see 21 CFR 172, 21 CFR 184, and 21 CFR 570.35). DL-methionine is unique among amino acids cleared for food use in that it is the only one listed that explicitly says it is not for use in infant feed formulas (21 CFR 173.320). When heated to decomposition, methionine emits dangerous and highly toxic fumes (NIEHS, 1999).

(5) The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock.

Although methionine is nutritionally essential for all mammals, it can be significantly toxic according to rat studies (Regina, 1992). In pigs, excess methionine can actually suppress weight gain (Baker, 1989). The rate of methionine depletion from tissue pools is high, therefore the potential for methionine wastage is high if supplementation of intact protein diets with pure sources in a once-a-day feeding regimen is employed. On the other hand, pure sources of amino acids are more bioavailable than intact-protein sources (Baker, 1989).

Amino acid requirements may be affected by environmental temperature extremes, basically because of the effect on feed intake, but amino acid supplementation will only affect weight gain if it improves feed intake. Methionine may range from first to third-limiting amino acid depending on the species, stage of production, and type of diet being supplemented (Baker, 1989).

For ruminants, the factors affecting the benefit of amino acid supplementation become even more complex due to the fact that 70% of bovine protein synthesis is a result of microbial conversion. Moreover, unprotected forms of methionine, such as DL-methionine, will be degraded in the rumen although it may still have a positive effect on enhancing microbial synthesis. Nonetheless, research continues on ways to protect DL-methionine such as with coatings of synthetic plastics or zinc methioninate complexes. Whenever certain factors change--species, age, environmental conditions, level of performance, energy content of the feed, vitamin dosing--the amino acid requirements of the animal change as well (Degussa, no date).

Intensive animal production leads to the inefficient utilization of nitrogen in feed and hence its waste in animal excreta. Supplementation with amino acids, especially synthetic ones which are absorbed more rapidly, may counteract this loss. However, amino acid losses from the rumen in dairy cattle may indicate that this benefit is more likely to be seen in pigs and poultry (Tamminga and Verstegen, 1992). Nonetheless, livestock management modifications such as more efficient use of animal excreta, i.e. manure, or less intensive animal production could also counteract this problem.

Managing the nitrogen cycle is seen as a challenge to livestock producers (Tamminga and Verstegen, 1992; Tamminga, 1992; Morse, no date). Poultry layer operations are experiencing increased costs and regulations for manure management (Sloan, et al., 1995). Supplementation with amino acids may allow dietary protein and excretory nitrogen levels to be reduced with a minimum reduction in egg output (Summers, 1993; Sloan et al., 1995). Amino acid supplementation is not the only means identified to reduce nitrogen pollution from animal manure. Other potential solutions include lower animal densities; more frequent rotations; better manure storage, handling, and application techniques; use of enzymes; improved processing of the feed; and selection of more appropriate land and locations to graze and shelter animals (Archer and Nicholson, 1992; Tamminga, 1992; Tamminga and Verstegen, 1992; Bedford, 1995).

(6) The alternatives to using the substance in terms of practices or other available materials.

The production factors cited as reasons to supplement limiting amino acids may be addressed by changes in animal and land management practices, novel feed sources, and better feed handling. Methionine is also found in naturally occurring proteins. Alternatives include improved pasture management, a balanced supplemental ration composed of organic grains, legumes, and oilseed meals. Feed sources with high percentages of methionine are bloodmeal, fish meal, corn gluten meal and sunflower seed meal. In ruminants, sources of mineral sulfur such as gypsum and epsom salts can be coverted to methionine (National Research Council, 1989). Natural sources of essential amino acids and appropriate feed regimens exist to assure adequately balanced rations. DL-methionine is one of the few amino acids not able to be produced economically by fermentation (Areki and Ozeki, 1991). It seems unlikely that a non-synthetic, non-GMO source of isolated L-methionine will be commercially available at a cost competitive with organic feed.

It appears to the investigator, and to two of the three reviewers that all essential amino acids are available in organically grown feed in quantities sufficient to ensure a balanced diet. This is true of methionine as much as any other amino acid. Methionine is seldom considered limiting in ruminants given the ability of the rumen to metabolize other forms of sulfur into methionine and other sulfur amino acids (National Research Council, 1989; van Soest, 1982). While certain amino acids may be able to enhance production, it remains to be proven that basic animal nutritional needs are not met by organic sources or that health-threatening amino acid deficiencies will result from the withholding of synthetic amino acids. The National Academy of Sciences reports that "[t]he greatest disagreement concerning amino acid requirements for broilers centers on the sulfur amino acids, methionine and cystine" (National Research Council, 1994). Some poultry nutrition researchers consider the claim that methionine is the first limiting amino acid to be unsubstantiated and in need of further investigation (Fisher, 1994). Even chicks that are marginally deficient in methionine will show little difference in weight gain from those fed on an adequate diet (Buttery and Boorman, 1976). Cystine and cysteine compliment methionine in that a certain amount of methionine will be converted into those other sulfur amino acids if necessary. In many cases, methionine requirements are overestimated because assays do not accurately reflect the amounts of cystine and cysteine precursors in practical diets (Baker, 1989).

Other cases have shown significantly higher weights and faster gains from amino acid (lys+met) supplementation (Slominski et al, 1999). Also, the digestibility of practical ingredients, such as corn and soybeans, appears to be on the order of 85% or more (National Research Council, 1994).
Rice and casein offer potential novel available sources of methionine (Lewis and Bayley, 1995). Yeast protein has long been known as a rich protein source relatively high in methionine+cystine (Erbersdobler, 1973; National Research Council, 1994), as well as phosphorous and B-complex vitamins (Morrison, 1951). Other potential sources of available methionine for poultry appear to be sunflower meal and canola meal (Waibel et al., 1998). Optimally balancing these nutrients may be challenging to feed processors and livestock producers.

The NOSB may also want to discuss and consider the role of animal protein in the diets of poultry. Hens on good pasture have no need for protein supplements of animal origin (Morrison, 1951). Pasture quality will vary according to field conditions and the season. However, free range poultry on well managed pasture are able to supplement their diets with insects, annelids, and fresh green forage (Smith and Daniel, 1982). Temporarily confined poultry can be fed practical organic corn / soybean ration. Depending on how other parts of the standards evolve and market conditions, novel organic products can be developed as supplements. Among the potential alternative sources include organic dairy products such as casein, organic meat by-products, and--assuming organic fish standards--organic fish meal (National Research Council, 1982 and 1994).

Macroorganisms commonly found in healthy pasture soils cannot be discounted as a source of nutrient cycling in free-range poultry systems. Given the natural feeding habits of poultry and other birds, the use of earthworms is a logical source of protein in chicken feed (Fisher, 1988). Earthworm populations of pasture depends on a number of factors (Curry, 1998). The amino acid content of earthworms will vary depending on species and food source. However, earthworms have been found to accumulate and concentrate methionine found in the ecosystem in proportions greater than for other amino acids (Pokarzhevskii, et al., 1997). As a feed supplement, earthworms have been found to equal or surpass fish meal and meat meal as an animal protein source for poultry (Harwood and Sabine, 1978; Taboga, 1980; Mekada et al., 1979; and Jin-you et al., 1982 all cited in Edwards, 1998).

Earthworms can play a role in moderating nitrogen losses as well (Blair, et al., 1997). Enzyme treatment of feedstuffs can improve amino acid availability and also reduce nitrogen pollution (Tamminga and Verstegen, 1992), as can changes in stocking density, rotations, and manure handling.

The therapeutic uses of different amino acids also have a number of alternatives. Given that most of the treatments are to treat nutritional disorders, alternative programs of prevention and treatment will often be based on better diet. Uroliths appear to be more common in carnivorous companion animals such as dogs and cats than in herbivorous / more omnivorous farm animals. They tend to be related to acid-base balance in the rations and excessive calcium and / or magnesium relative to other cations in the diet. Ammonium chloride is another synthetic substance commonly used to acidify urine, but sodium chloride (common salt) may be used to treat urinary tract calculi in sheep (Aiello, 1998). Hepatic lipidosis is a condition of excessive fat in the liver commonly associated with caged birds and is related to the fact that wild diets are much lower in fat than seed diets fed to captive species (Aiello, 1998). A diet that has less fat and living conditions that allow birds to exercise more appears to be a practical, viable alternative. Enteritis is a disease frequently observed in poultry that do not have access to the soil and green growing plants (Titus, 1942). Well managed pasture would prevent this cause of the disease.

(7) Its compatibility with a system of sustainable agriculture.

The feeding of isolated amino acids produced by the use of non-renewable fossil fuels and toxic chemicals is not compatible with a system of sustainable agriculture. Synthetic amino acids increase animal production by lowering feeding costs, overcoming nutritional and stress related diseases associated with confinement, and reducing manure output. While this is not by itself unsustainable, amino acids thus facilitate high-input concentrated confinement animal production seen as antithetical to sustainable agriculture. Most importantly synthetic amino acids discourage the integration of a whole-systems approach to cycling nutrients, particularly nitrogen, as part of an integrated crop-livestock production system.

Increased efficiency of protein conversion reduces the amount of nitrogen excreted (Summers, 1993; deLange, 1993). The cycling of nutrients from animals is part of an integrated farming system, and the environmental effects of manure management requires looking at the big picture (Archer and Nicholson, 1992). What is viewed as a liability in confinement animal systems--nitrogen production--is seen in cropping systems as a limiting factor resource. Reduction of nitrogen pollution may require improved range or pasture management, and with that either more frequent rotations or lower stocking rates.

Discussion

Condensed Reviewer Comments

None have a direct commercial or financial interest in enzymes in general or bromelain in particular. Reviewer 1 is a consultant in animal nutrition; reviewer 2 is a veterinarian and pharmacology researcher; reviewer 3 is a professor of food science.

Reviewer 1
I agree with what is proposed but think it should be expanded to indicate that methionine or an amino acid can be added in amounts necessary so that the diet meets the animal's nutritional requirements. When a produced substance is identical chemically to that which occurs naturally I think that produced should be considered non-synthetic. I believe this is the case for methionine, as well as other amino acids. Therefore I believe they should be considered non-synthetic. Their production however, may not be compatible with organic purposes and standards.

I believe their use to meet the animals nutritional requirements for optimum health and performance should be allowed, if they are obtained from organic feedstuffs or in a manner compatible with organic status. As such I disagree with what is stated in this section after OFPA that amino acids "may be considered prohibited as a growth or production promoter and therefore prohibited in livestock production for such purposes".

Based on medical (versus nutritional) uses, as indicated previously for methionine, and those for the non-essential amino acid glutamine for conditions in which enteritis is present, I would add the following to this section. . . . 'While amino acids have a number of functional uses in animal production their primary purposes are to enhance production with a lower costing diet, or with some amino acids to assist in the management of certain diseases (e.g. urolithiasis, hepatic lipidosis and those in which enteritis may be present).'

. . . 1) I think an artificially produced substance identical chemically to that which occurs naturally should be considered non-synthetic. This does not imply that all means of its production are acceptable and therefore that the substance is acceptable and can be used, but that it is indistinguishable from that occurring naturally, and 2) methionine, or any amino acid or nutrient, whose addition to the diet enhances growth would do so only if it helped correct a nutritional deficiency for that particular animal or situation. In addition an amino acid is not a synthetic growth promoter; it is a nutrient whose addition to the diet promotes growth only if it were deficient in that diet. Amino acid supplementation would enhance growth when a growth promoter was used only if the growth promoter stimulated growth in excess of what the diet provides without its addition, i.e. the growth promoter increased the animal's requirement for that nutrient in excess of what was in the diet. . . This . . . should relate to all amino acids, essential or non-essential (e.g. glutamine).

[In reference to the statement] "Suitable uncontaminated pasture and exposure to sunlight can provide all the protein and vitamins laying hens require (Morrison, 1951)."
Comment: This depends on the pasture forage type and season but generally it is not true. Certainly many pastures and during many seasons do not provide the 15% protein, 0.53% methionine plus cysteine, 0.5% lysine, 2.85 Mcal/kg, 2.75% calcium or 0.6% phosphorus required for laying hens or the 20% protein, 0.75% methionine plus cysteine, 1.1% lysine or 2.9-3.2 Mcal/kg needed for growth (NRC).

Rice groats, sunflower seed meal and fish meals are particularly high in the sulfur containing amino acids, methionine plus cysteine (5.85, 4.7 and 4.7% of their protein, respectively), followed by rice, casein, skim milk, whey, cottonseed meal and rape or canola seed meal (3.7 to 3.9% for all) (NRC, Nutrient Requirements of Dogs, Table 8, 1985), as compared to requirements of 3.5 to 3.7% for poultry, 2.8% for swine, 2.4% for dogs, 3.6 to 4.2% for cats and none specified for ruminants or horses (NRC and AAFCO).

Optimally balancing these nutrients may be challenging to feed processors and livestock producers. The NOSB may also want to discuss and consider the role of animal protein in the diets of poultry, although animal tissues contain less methionine plus cysteine than needed (2.8 to 3.3% of their protein versus 3.5 to 3.8% needed in their diet). Hens on good growing pasture containing some legumes may not need more protein (Morrison, 1951), but may need more methionine plus cysteine, since both grass and legume forage contain less than that needed (2.0 to 3.1% of their protein versus 3.5 to 3.8% needed). Organic fish meal (assuming organic fish standards), organic dairy products, as well as slaughter by-products from organic meat may offer potential sources to balance amino acids in a practical corn / soybean meal ration (which contain 2.0% in corn and 2.8% in soybean meal of their protein as methionine plus cysteine).

<Note regarding Reviewer 1
In a phone coversation following the review, Reviewer 1 said that he did not know of any naturally occurring source of the racemic mixture of DL-methionine. Such as specific mixture would be synthetic in his opinion. However, he believes in general that source or manufacturing process is not relevant to determining whether or not a substance is synthetic or non-synthetic. He acknowledged that amino acids could be synthesized outside of biological processes, but as long as they were chemically indistinguishable from those isolated from natural sources, they were 'non-synthetic' regardless of the source. >

Reviewer 2
This is a synthetic substance in that its commercial manufacture involves not only chemical extraction but reaction and conversion as well. While organic farming is based on certain principles, it is also an art and shouldn't be overly restrictive as far as individual practices that a particular farmer may want to utilize as long as they do not conflict with those principles. Substituting a synthetic essential nutrient source for naturally derived ones seems to be such a conflict. Therefore, methionine should only be allowed as long as it is from organically produced sources and does not contain any toxic contaminants as a result of the chemical processing which renders it synthetic. Furthermore, the protocol and reasons for its use should be noted in the farm plan along with steps taken to eliminate reliance on amino acid supplementation.

Reviewer 3
Methionine is one of the sulfur containing amino acids used as a feed supplement to balance nitrogen metabolism and enhance weight gain. The L and D forms of amino acids may not have the same physiological characteristics and effects (DeGussa, no date). For methionine, its chemical synthesis results in a racemic mixture of 50% D and 50% L forms. Additionally according to Degussa the D form (non-biologically active) can be converted to the L form (i.e. biologically active) via an amino acid oxidase enzyme system by oxidative deamination and subsequent transamination reactions in organisms. This reference does not state for what animals this may occur. If it does occur in all animals as the paper suggests on page 14, is 100% of the D form converted to the L form? This is not clear. The D form of lysine can not be converted to the L form in animals and therefore can not be utilized. I feel this is important because all synthetic methionine is in a racemic mixture and little is known concerning the projected benefit based on the stoichiometry of the coupled deamidiation- transamination reaction invivo.

From the literature, several studies have shown that feed rations can be engineered to enhance animal nutrition and subsequent weight gain and performance (Waibel, et al., 1998). In a review paper by Baker (1989), he describes a transition by animal nutritionists to formulate diets on an amino acid rather than a protein basis. Overall, there seem to be more questions than scientifically proven facts regarding the over all use, level, effects of environment, species, gender and other variables to accurately predict the positive benefit of amino acid supplementation.

From the studies and information presented to date, DL methionine is clearly synthetic. . . . [A] well-balanced animal feed ration coupled with well-managed organic pasture preclude the need or necessity to supplement animal feed. I also feel that the addition of synthetic DL racemic mixtures of any amino acid is not compatible with organic agriculture. Additional research should be conducted to evaluate the potentially positive effects of amino acid supplementation on agro ecosystem issues of water and air pollution. However, this is a complex issue and it is difficult to extrapolate the effects of one of many variables (i.e., synthetic amino acids). Additionally, I agree with the reference (Morrison, 1951) that suitable uncontaminated pasture and exposure to sunlight can provide all the protein and vitamins laying hens require. I concur with the discussion section of the NOSB materials database.

In the quest for more rapid weight gain over shorter times conventional farming has sought to increase animal weight gains and overall productivity by optimizing each nutrient to create a synthetic formulation to reduce overall economic issues. Therefore I feel this approach (synthetic amino acid feed supplementation) is simply not compatible with sustainable agriculture. In summary, I do not recommend that synthetic methionine in all its forms be added to the National list of Allowed Non-organic Ingredients for Animal Feed Stuffs.

Conclusion

Farm animal diets formulated based on amino acid content rather than protein content is a relatively recent phenomenon. Animal nutritionists have been making the transition over only the past 20 years (Baker, 1989). Amino acids are essential for animal nutrition and do not need to be derived from non-organic or synthetic sources (Morrison, 1951). Synthetic amino acids used as feed supplements have many parallels to synthetic nitrogen sources for plant foods. Animal nutrition studies have embarked on a reductionist paradigm that does not take into account the ecology of the animals and their interaction with other components of the entire farming system. Even those who conduct the research in such systems acknowledge the limitations of the ability of model feed rations to capture the complexity of animal nutrition (see, for example, Buttery and D'Mello, 1994).

By substituting a non-renewable synthetic input for organically grown crops as a source for nutrition, synthetic amino acids would thus reduce the amount of acreage planted to organic feed and forage crops. Farmers who seek organic certification have less of an incentive to provide clean, fresh pasture as a primary source of animal nutrition if they have available synthetic amino acids. Use of dietary manipulation to reduce nitrogen excretion is an artifact of high-input confinement systems divorced from a holistic farming system. Isolated amino acids should not be allowed to substitute for organically grown grains, well managed pasture systems, and sound programs for manure management.

Experts disagree on the need and efficiciencies of supplementation. While there is need for a great deal more research and there are limitations to extrapolating across species, the debate between the nutritional value of pure or intact food remains unsettled. A recent study of 46 supplements for the quality of their antioxidants composition demonstrated that natural intact food sources were better (Tufts, 1999).

In summary, to be certified as organic, the Technical Advisory Panel recommends that livestock obtain their amino acids from protein sources that meet organic standards. Such a conclusion and recommendation appears outside the scope of the National List, and requires no action on the part of the NOSB. The NOSB may want to consider amending the livestock feed standards to explicitly make it clear that proteins and amino acid sources fed to organic livestock must be produced and processed according to certified organic standards.

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Amino Acids

Processing

Identification

Chemical Names L-cysteine, Cys, L-cysteine monohydrochloride

Other Names: Cysteine is the model amino acid used for the purpose of this review. Much of the supporting data is for L-cysteine monohydrochloride. See attached list.

CAS Numbers:
L-cysteine monohydrochloride: 52-89-1

Other Codes:
L-Cysteine EU 920
[INS number expected to be the same, no separate number for the monohydrochloride salt].

Recommendation

Synthetic / Non-Synthetic:	National List:	Suggested Annotation:
Synthetic (consensus)	*Not Allowed 95%+ (consensus)* *Not Allowed 50% + (2-1-1)*	*Prohibited as an ingredient in organic food. (3-0-1).* *Prohibited as an ingredient in foods made with organic ingredients (2-1-1).*

Characterization

Composition:
Amino acids have an amino group (NH_2) adjacent to a carboxyl (COOH) group on a carbon. The formula for L-cysteine is $H_2NSCH_2CHCOOH$ and for L-cysteine monohydrochloride is $H_2NSCH_2CHCOOH \bullet HCl \bullet H_2O$ or $C_3H_2NO_2S \bullet HCl \bullet H_2O$

Properties:
Amino acids are the building blocks of proteins and peptides. As such, they are naturally occurring, but are rarely found in free form. Not all amino acids are associated with formation of proteins and there are a considerable and growing number of non-protein amino acids that are not found in nature. L-Cysteine monohydrochloride is a white odorless crystalline powder having a characteristic acid, slightly sweetish taste. Soluble in water and alcohol. Melting point 175°C.

How Made:
Amino acids can be produced from a number of different sources by a wide variety of means. One biological source is the extraction of keratin from human hair by use of hydrochloric acid and water. After several steps (not disclosed), keratin is hydrolyzed and purified into L-cystine (Sun-Orient Chemical Co., Ltd., 1998). L-cystine is then dissolved into a hydrochloric acid solution and converted by electrolysis to L-cysteine monohydrochloride in several steps (Sun-Orient Chemical Co., Ltd., 1998).

DL-cysteine hydrochloride can also be produced from the reaction of ammonia, hydrogen cyanide and mercaptaldehyde in the Strecker process (Ashford, 1994). DL-cysteine can then be resolved into L-cysteine and D-cysteine enantiomers (Streetweiser and Heathcock, 1985). L-cysteine can also be produced by the reaction of chloroacetaldehyde with hydrogen cyanide, ammonium bicarbonate, and sodium sulfide in the Bucherer-Berg reaction (Ashford, 1994). L-cysteine can be crystallized into the monohydrochloride form by reaction with a solution of hydrochloric acid. L-cysteine monohydrochloride can also be produced by an enzymatic process (Ashford, 1994).

In any case, the hydrochloride salt of L-cysteine would be considered synthetic given the crystallization product of reacting hydrochloric acid.

Furthermore, there are increasing numbers of cases where amino acids can be derived from genetically-engineered organisms; these products are to be considered synthetic, per NOSB determinations on genetic engineering. They also may be synthesized by a variety of other chemical means, and in these cases, would also be considered synthetic.

Specific Uses:
Amino acids have a wide range of uses in food processing and handling: as nutrients, dietary supplements, flavor enhancers, salt substitutes, coloring aids, anti-oxidants, preservatives, texturizers, dough conditioner or strengtheners. The model amino acid for this review, L-cysteine monohydrochloride, is used as a dough conditioner and as an anti-oxidant. When L-cysteine monohydrochloride is heated with sugar, it is used to form a broiled beef aroma extract (O'Hara, 1974). All protein and many non-protein amino acids are used in processing (see Winter, 1989; Food Chemicals Codex, 1996). The most used amino acids in processing are glutamic acid and its salt, monosodium glutamate (MSG) (Araki and Ozeki, 1991). Another familiar amino acid product is aspartame, the dipeptide ester formed as a combination of aspartic acid and phenylalanine. Aspartame is used as a sugar substitute (Winter, 1989).

Action:
In general, amino acids have many modes of action based on their ability to form proteins and impart flavors. L-cysteine hydrochloride acts as an antioxidant by a reduction reaction in ascorbic acid fortified foods (O'Hara, 1974). Ascorbic acid need not be present to prevent browning, but the two antioxidants act synergistically.

Combinations:
Amino acids are used in literally hundreds of combinations. The model amino acid used in this review, L-cysteine monohydrochloride, is most effective in low-pH solutions with a food grade acid.

Status

OFPA
Amino acids, generally and specifically, would be considered non-synthetic, non-organic ingredients used as a direct food additive (7 U.S.C. 6518(c)(1)(B)(iii)).

Regulatory
Regulated by the Food and Drug Administration. See discussion of GRAS listing below.

Status among Certifiers
In general, amino acids have been a gray area in organic processing standards. While most would prohibit MSG or aspartame as clearly synthetic, various certifiers have considered some amino acids to be non-synthetic and allowed for post-harvest handling uses, as processing aids or as non-organic ingredients. For example, L-cysteine monohydrochloride was implicitly allowed by California Certified Organic Farmers, Oregon Tilth, and other certifiers for post-harvest handling of fresh produce between 1994 and 1997. The substance was removed from their lists and placed under consideration in 1997.

Historic Use
Provisionally allowed by various certifiers under the assumption that they were 'natural' and not available from an organic source.

International
The Codex Alimentarius Commission organic food guidelines say that amino acids may be used as a food additive "[o]nly approved in so far as their used is legally required in the food products in which they are incorporated" [sic] (Joint FAO/WHO Food Standards Programme, 1999). L-cysteine was added the European Union list of approved food additives--for all foods, not just organic foods--in October 1998 by Directive 98/72. Does not appear on the EU list of approved substances to be used as direct food additives in organic foods. IFOAM does not list amino acids as allowed in processing, either individually or collectively (IFOAM, 1998).

OFPA 2119(m) Criteria

(1) The potential of such substances for detrimental chemical interactions with other materials used in organic farming systems. As this is a processing material, the substance is not used in organic farming systems.
(2) The toxicity and mode of action of the substance and of its breakdown products or any contaminants, and their persistence and areas of concentration in the environment. See processor criteria 3 below.
(3) The probability of environmental contamination during manufacture, use, misuse or disposal of such substance. This is considered below under item (2).
(4) The effect of the substance on human health. This is considered in the context of the effect on nutrition (3) below as well as consideration of GRAS and residues (5) below.
(5) The effects of the substance on biological and chemical interactions in the agroecosystem, including the physiological effects of the substance on soil organisms (including the salt index and solubility of the soil), crops and livestock. As this is not released into the agroecosystem, there is no direct effect.
(6) The alternatives to using the substance in terms of practices or other available materials. See discussion of alternatives in (1) below.
(7) Its compatibility with a system of sustainable agriculture. This is considered more specifically in the context of organic handling in (6) below.

NOSB Processing Criteria

A SYNTHETIC PROCESSING AID OR ADJUVANT may be used if;

1. An equivalent substance cannot be produced from a natural source and has no substitutes that are organic ingredients.

   Fresh organic produce does not necessarily need preservative or anti-oxidant additives. Picking to order, more frequent and more timely shipment, tighter inventory managment, better management of product flow, maintaining temperatures, and rotating stock can compensate for shorter shelf life.

   The anti-oxidants ascorbic acid, citric acid, and tocopherols (Kays, 1991) are already recommended to be added to the National List. Other antioxidants not yet reviewed by the NOSB include the following GRAS substances: sulfites, cinnamic acid, benzoic acid, carbon monoxide, EDTA, glutathione, N-acetylcysteine and inorganic halides.

   There are a number of potential alternatives to the use of L-cysteine monohydrochloride that can be used to prevent browning in potato processing. Some approaches include variety selection, quality assurance of lower reducing sugars, and holding the potatoes longer at elevated temperatures to convert more sugars to starch may all be viable alternatives. Ascorbic acid and citric acid are used as anti-browning agents, most widely for enzymatic browning in fruit and vegetable processing. Additionally, exclusion of oxygen also helps in reducing the rate of enzymatic browning.

   Tocopherol, derived from non-GMO, non-solvent extracted soybeans, can be used in a wide variety of cereal and bakery products as an anti-oxidant (i.e., slow down the rate of lipid oxidation) as a function of processing and storage. Again, exclusion of O2 can also slow down the rate of lipid oxidation (i.e., muscle foods, foods with high level of unsaturated fatty acids).

   Good baking techniques will produce acceptable quality dough for most uses. Increased mixing time will yield comparable results (Sai Manohar, R. and Rao Haridas, P, 1997). Other compounds that are more acceptable exist, be they oils, natural emulsifiers, or other agricultural products, such as gluten (Saiz, et al. 1997).

2. Its manufacture, use and disposal does not contaminate the environment.
   Depending on the amino acid in question, and the particular process to produce it, there may be some environmental and/or human safety hazards associated with the manufacture of these materials.

   For the case of cysteine, hydrochloric acid is hazardous to handle and use; synthetic alternatives for production of this amino acid are even more hazardous (involves hydrogen cyanide). The degree of negative impact(s) of amino acid production varies, and these may have to be evaluated on a case-by-case basis, if they are to be allowed at all. The main concern with manufacturing from human hair is the use of hydrochloric acid. Hydrochloric acid is highly corrosive (Sax, 1984). Hazards when working with the substance include explosions, lung injury, edema, severe burns, and death (NIEHS, 1991). The by-products of processing the human hair is disposed of in a manner similar to other biological wastes (Skymart Enterprises, 1994).

   Hydrogen cyanide is produced by further processing of methane and ammonia. Hydrogen cyanide is a gas that is highly toxic. Exposure causes paralysis, unconsciousness, convulsions, and respiratory arrest. Death usually results from exposure at 300 ppm concentrations for a few minutes (Clayton and Clayton, 1982). Hydrogen cyanide has a toxicity rating of 6 and is one of the fastest poisons known to man (Gosselin, 1984). Manufacture of hydrogen cyanide is a significant source of atmospheric release of cyanide (Midwest Research Institute, 1993).

   Misuse of amino acids, as far as undue levels accidentally being ingested, can be a concern; toxicity varies from one to another and affects some people more than others. Overall, the risks of overexposure to amino acids themselves, however, should be minimal, as long as good manufacturing practices are used and quality assurance and HAACP programs verify that such practices are maintained.

   Disposal of amino acids into the environment should not pose any significant risk.

3. If the nutritional quality of the food is maintained and the material itself or its breakdown products do not have any adverse effect on human health.

   The introduction of essential amino acids could potentially enhance the nutritional quality of the food from a narrow, empirical perspective. The model amino acid, L-cysteine monohydrochloride, is not considered essential, and is easily synthesized. The LD50 of L-cysteine monohydrochloride is 1250 mg/kg (mouse) (Areki and Ozaki, 1991). Lethal doses fed to rats and mice caused ataxia, sedation, decreased activity, reflex reduction, muscle relaxation, respiratory depression, hypothermia, and apparent congestion of several organs (Takaski, et al., 1973 quoted in Environ, 1987). Cysteine treated mice developed retinal and hypothalmic lesions identical to those associated with MSG (Olney and Ho, 1970).

   Exposure to free amino acids in pure available form have been long been linked to a number of genetic disorders and food allergies. The most widely studied are those related to glutamic acid and glutamates, in particular MSG. Also, the link between phenylalanine and phenylketonuria has also been the subject of much study. While such problems associated with the cysteine are less common and have not been exhaustively studied, they are nonetheless documented. Free cysteine can cause problems in a segment of the population. Cystine--a metabolic product of cysteine--has been linked to cystinuria (Meister, 1965). Individuals who suffer from cystinuria accumulate amino acids in the urine and the formation of kidney stones composed of cystine (Environ, 1987). More common in the literature are allergies to cysteine-based proteins that are activated by cysteine proteases, such as bromelain (see, for example, Pike, Bagarozzi and Travis, 1997).

   Addition of amino acids to food products could conceivably boost nutritional value, from a purely analytical viewpoint, as certain amino acids are lacking in certain foods (or certain regional diets). However, in the absence of solid evidence that there is a real nutritional deficiency in the target population for the food product(s) in question, precautionary action on the part of the food manufacturer is warranted.

   It is safer to avoid addition of amino acids under normal circumstances. Research is incomplete on the role free amino acids play in the human system. They can serve as neurotransmitters or precursors of neurotransmitters, and altering the balance of them as compared to a natural human diet may have unknown or negative effects. A common example is the effect of monosodium glutamate and D-glutamate on certain individuals (Coyle and Puttfarcken, 1993). High bloodstream levels of tryptophan can alter sleep cycles due to its impingement on serotonin production. Other amino acids have been linked to genetic disorders, such as phenylalanine in phenylketonuria, and cystine in cystinuria. These are only some of the possible range of action of amino acids in the human system. A related example is aspartame, a dipeptide of aspartic acid and phenylalanine used as a sweetener; health questions have been raised about the safety of this food additive (Winter, 1989).

4. Is not a preservative or used only to recreate/improve flavors, colors, textures, or nutritive value lost during processing except in the latter case as required by law.

   By delaying oxidation and extending product shelf life, L-cysteine monohydrochloride could be considered a preservative. It is debatable whether cysteine used as an anti-browning agent in dehydrated potatoes could qualify it as a preservative, or at least as a means of retaining color otherwise lost during processing. Decomposing cysteine used as beef aroma / flavoring agent would be considered a way to artificially recreate flavors. Cysteine improves dough quality by working on the gluten as an antioxidant (Koh, et al, 1997).

5. Is Generally Recognized as Safe (GRAS) by FDA when used in accordance with Good Manufacturing Practices (GMP), and contains no residues of heavy metals or other contaminants in excess of the tolerances established by FDA.

   The Food, Drug, and Cosmetic Act, 21 CFR Sec. 172.320(a) lists that food additive amino acids may be safely used as nutrients added to foods. The list includes both L-Cysteine and L-Cysteine Monohydrochloride. Section 172.320(c) establishes that amino acids used as an additive "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 . . .
   (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.

   "The amount of the additive added for nutritive purposes plus the amount naturally present in free and combined (as protein) form cannot following levels of amino acids expressed as percent by weight of the total protein of the finished food [sic]. For example, the maximum percent by weight of total protein in a given food expressed as free L-cysteine and L-cystine expressed as free amino acid is 2.3%."

   The regulations further state that "[e]ach 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 required 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 and Human Services 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." The regulations go on to state the specific content of the records required to be kept.

   Additionally, specific regulations regarding L-Cysteine monohydrochloride are found at 21 CFR 184.1272. These state that the ingredient may be used to supply up to 0.009 part of total L-cysteine per 100 parts of flour in dough as a dough strengthener . . . in yeast-leavened baked goods and baking mixes. This regulation was issued prior to a general evaluation of use of this ingredient in order to affirm as GRAS the specific use named. Use as an antioxidant in fresh produce is not mentioned but appears to be covered as part of the general evaluation.

Food Chemicals Codex limits: Must contain not less than 98.0% and not more than 102.0% of $C_3H_2NO_2S{\bullet}HCl{\bullet}H_2O$after drying. Arsenic as As not more than 3 ppm; heavy metals as lead (Pb) of not more than 0.002% and lead not more than 10 ppm, loss on drying not less than 8% and not more than 12% (National Academy of Sciences, 1981 et seq).

6. Is compatible with the principles of organic handling.

   In general, the use of isolated amino acids does not appear to be compatible with organic handling to most if not all of the reviewers. Use to extend shelf-life appears to be counter to consumer expectations that organic produce is fresh and does not have any artificial preservatives. Use to fortify foods also does not appear to be compatible. There is no product formulation or recipe known that absolutely requires their inclusion, and no process that is rendered impossible by their exclusion. Preservative action, mimicking of flavors, creation of non-essential food product characteristics, or re-creation of sensory qualities by such isolated, non-organically-produced materials runs counter to the principles of organic handling. Additionally, organic foods should not contain artificial flavors or synthetic flavor potentiators. On that basis, L-cysteine and other amino acids are not compatible as organic flavor enhancers. Supplement of diet by amino acids runs counter to the principle that proper nutrition can be achieved through a varied, wholesome diet.

7. There is no other way to produce a similar product without its use and it is used in the minimum quantity required to achieve the process.

   For L-Cysteine: Use of an antioxidant is not essential for fresh produce. Dough conditioners are not essential for flour. Artificial beef aroma is not essential for any food. Because L-cysteine is not an essential amino acid, no food needs to be fortified with it. As nutritional supplements in general, isolated amino acids are not organic ingredients, and so should not be added to foods labeled as organic. Therefore the minimum amount required for use in such foods would be zero. In general: the reviewers could find no food product, legal requirements, or standards of identity where amino acids were required to produce a given food.

Discussion

Condensed Reviewer Comments

None of the reviewers had a commercial or financial interest in L-cysteine monohydrochloride or any other amino acid.

Reviewer 1
Amino acids may be synthetic or non-synthetic, depending on their source, means of isolation, and final molecular structure. Classification as synthetic or non-synthetic therefore needs to be determined on a case-by-case basis.

In all cases, it is recommended that amino acids be PROHIBITED for inclusion in any foods labeled as organic. In foods which are labeled as "made with organic ingredients," it may be possible to allow non-synthetic amino acids to be used as non-organic ingredients, but with the restriction that the product label specifically explains the purpose of their use in the product. Otherwise, the likelihood of confusing the consumer is too high. This restriction should be added to the proposed annotation given in the NOSB database, which otherwise seems complete.

It should be reiterated that the above allowance only applies to non-synthetic amino acids. Synthetic amino acids, including those which are products of genetic engineering should be PROHIBITED in any foods containing organic ingredients.

Reviewer 2
I would consider that all manufacturing processes for L-cysteine result in the formation of synthetic L-cysteine and/or the hydrochloride form. Even though hydrochloric acid is used, probably at a 6 normal or greater concentration, it is not produced by enzymatic proteolysis as cysteine is released in vivo. For example, humans have approximately 2N hydrochloric acid in their stomach that maintains the optimum pH for enzymes like pepsin and others to hydrolyze food proteins into their constituent amino acids so that they can be absorbed.

When conducting amino acid analysis in the laboratory, many methods use 6 Normal hydrochloric acid to hydrolyze the protein with no enzymes because the process is much faster and less expensive. Therefore, any amino acid produced as a function of 6N Hydrochloric acid hydrolysis is synthetic.

In summary, I feel that all commercial methods as provided by the NOSB database and from my sources indicate that L-cysteine is synthetic. Because of the issues of alternatives, incompatibility with organic process criteria, potential for loss of vitamin B6, as well as NOSB processing criteria 3, I recommend that L-cysteine or L-cysteine hydrochloride not be added to the National List of Allowed Non-organic Ingredients.

Reviewer 3
I believe that the NOSB should recommend that amino acids be restricted for usage in foods made with organic ingredients, only in a case-by-case basis for specific uses. There may be cases of essential amino acid fortification, for example, that may make sense for certain population groups. The NOSB should also specifically restrict the usage of any amino acids made from genetic engineering, racemic mixtures, and D-enantiomers. The use of monosodium glutamate and other “free” glutamates should be prohibited in organic foods.

Reviewer 4
L-cysteine hydrochloride and ascorbic acid are both antioxidants (preventing browning) and do not need to be used together. They often are, but this is not required. L-cysteine hydrochloride is a sulfhydryl containing amino acid which prevents browning by reacting with quinone intermediates in the browning reaction catalyzed by the enzyme, polyphenol oxidase.

Alternatives to L-cysteine as an antioxidant include the following (all are GRAS): ascorbic acid, citric acid, sulfites, cinnamic acid, benzoic acid, carbon monoxide, EDTA, glutathione, N-acetylcysteine and inorganic halides. Use of cysteine to prevent browning is not considered a preservative, it's more of a processing aid.

Conclusion

Unlike vitamins and minerals, the reviewers could find or cite no guidelines or laws that mandate the fortification of certain food products with amino acids at this point. Even if there were, it is highly unlikely that they would apply to a non-essential amino acid like L-cysteine monohydrochloride.

If the NOSB chooses to add amino acids to the National List, those foods that are artificially fortified may need to be labeled as "Made from organically grown ingredients and fortified with _____." The more difficult decision will be to determine whether or not amino acids in any form qualify to be used in foods labeled as made with organic ingredients. The NOSB might want to consider several different options. The most conservative approach would be to not allow such usage and require a case-by-case review. The most permissive would be to allow all amino acids from any source to be used in foods labeled as made with organic ingredients and as incidental ingredients of the non-organic ingredients on the National List. Amino acids essential for human nutrition are readily available in organically grown food. Restricted use of non-synthetic amino acids might be the most prudent course. The NOSB may want to explicitly exclude in the annotation those amino acids that are derived from genetic engineering, racemic mixtures, D-enantiomers, and monosodium glutamate.

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