Nature's One®
The Leader in Organic Medical Nutrition™

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April 4, 2016

Program Manager USDA/AMS/TM/NOP
Room 408-So., Ag Stop 0268
1400 Independence Ave. SW
Washington, DC 20250-0268

RE: Petition for inclusion of L-methionine on the National List at §205.605(b) as a synthetic non-agricultural substance allowed in or on nutritionally complete enteral pediatric formulas labeled as "organic" or "made with organic (specified ingredients)" with the annotation "for use in nutritionally complete pediatric enteral formula based on soy protein."

Dear Sir,

Nature's One, Inc. is a manufacturer of organic pediatric nutritional products. Nutritionally complete enteral pediatric formulas are used as oral or tube feedings to provide supplemental or total nutritional support to young children who are unable to consume their nutrition through foods due to various medical conditions.

At the October, 2012 meeting of the National Organic Standards Board, we requested the recommendation to allow L-methionine in soy-based infant formula products be amended to include nutritionally complete pediatric enteral products. This was denied with the request that we submit a separate petition to cover this needed area of pediatric medical nutrition therapy. We submitted a petition on March 29, 2013 and also responded to follow-up questions regarding the petition raised by the National Organic Program in subsequent communications. During our last communication with the National Organic Program held on March 9, 2016, we were asked to submit a new petition and to include the additional information provided through these subsequent communications since 2013.

It should be noted that during the May, 2012 meeting of the National Organic Standards Board, we had requested that the petitions for choline and inositol be amended to include not just infant formula but also pediatric enteral products. This request was addressed by the Board and was positively received.

This petition seeks to add L-methionine to the National List to permit its addition as a non-agricultural ingredient in nutritionally complete pediatric enteral formulas based on soy protein. L-methionine is an essential amino acid which the human body cannot make from other amino acids and which must be supplied from foods. This is especially important during the early years of growth and development in a young child's life, especially for children with medical conditions requiring total nutritional support and medical nutrition therapy. The biological value of soy protein is often inadequate to meet these growth and development needs unless supplemented with L-methionine. The addition of L-methionine improves the biological value of soy protein and prevents methionine deficiency.

Unlike soy-based infant formulas that must meet the U.S. Food and Drug Administration (FDA) regulation [21 CFR 107.100(f)] requiring the addition of L-methionine to satisfy the protein biological value of soy protein, nutritionally complete pediatric enteral products have no nutrient specific FDA

requirements. However, a sister agency to the FDA within the U.S. Department of Health and Human Services, the Centers for Medicaid and Medicare, has defined nutritionally complete pediatric enteral formulas through the Healthcare Common Procedure Coding System (HCPCS) and has assigned the code HCPCS B4159 to soy-based nutritionally complete pediatric enteral formulas. The definition is:

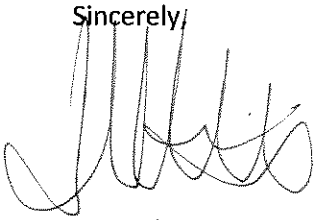
> "Enteral formula, for pediatrics, nutritionally complete soy based with intact proteins, including Proteins, fats, carbohydrates, vitamins and minerals, may include fiber, and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit."*

In addition, the FAO/WHO Codex Alimentarius Commission created a Codex Standard for pediatric nutritional enteral formulas (CODEX STAN 156-1987) which Codex refers to as "follow-up formulas." In the United States, the term "toddler formula" is used rather than "follow-up formula." Such formulas are also nutritionally complete pediatric enteral formulas. The standard requires a minimum biological quality of the protein in follow-up formula and also requires the L-form of an amino acid, including methionine. Also, the Committee on Nutrition of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) specifically set a minimum L-methionine level of 29 mg/100 kcal for follow-up formula based on soy protein. The addition of L-methionine to soy-based nutritionally complete pediatric enteral formulas is just as critical to young children as it is to infants, especially those who must receive the majority or all of their nutritional support from these products.

The October 24, 2011 petition for inclusion of L-methionine in infant formulas based on soy protein submitted by the International Formula Council (IFC) led to the recommendation for L-methionine in soy-based infant formula's inclusion on the National List by the National Organic Standards Board at its October, 2012 meeting. The IFC petition provided the necessary information on L-methionine required by the National Organic Program. We are using some of the information in this comprehensive and factual IFC petition to further support our petition in conjunction with our information on the need for L-methionine in nutritionally complete pediatric enteral products for children. Our petition and attachments provide the necessary information as required in the current Guidelines on Procedures for Submitting National List Petitions and satisfy the criteria in the OFPA.

Please contact us to provide any additional information if required to proceed with the review process and recommendation from the National Organic Standards Board.

Sincerely,



Jay Highman,
CEO &President
Nature's One, Inc.

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http://www.hipaaspace.com/Medical_Billing/Coding/Healthcare.Common.Procedure.Coding.System/B4159 Sourced: March 28, 2016

Unlike soy-based infant formulas that must meet the U.S. Food and Drug Administration (FDA) regulation [21 CFR 107.100(f)] requiring the addition of L-methionine to satisfy the protein biological value of soy protein, nutritionally complete pediatric enteral products have no nutrient specific FDA requirements. However, a sister agency to the FDA within the U.S. Department of Health and Human Services, the Centers for Medicaid and Medicare, has defined nutritionally complete pediatric enteral formulas through the Healthcare Common Procedure Coding System (HCPCS) and has assigned the code HCPCS B4159 to soy-based nutritionally complete pediatric enteral formulas. The definition is:

> "Enteral formula, for pediatrics, nutritionally complete soy based with intact proteins, including Proteins, fats, carbohydrates, vitamins and minerals, may include fiber, and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit."*

In addition, the FAO/WHO Codex Alimentarius Commission created a Codex Standard for pediatric nutritional enteral formulas (CODEX STAN 156-1987) which Codex refers to as "follow-up formulas." In the United States, the term "toddler formula" is used rather than "follow-up formula." Such formulas are also nutritionally complete pediatric enteral formulas. The standard requires a minimum biological quality of the protein in follow-up formula and also requires the L-form of an amino acid, including methionine. Also, the Committee on Nutrition of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) specifically set a minimum L-methionine level of 29 mg/100 kcal for follow-up formula based on soy protein. The addition of L-methionine to soy-based nutritionally complete pediatric enteral formulas is just as critical to young children as it is to infants, especially those who must receive the majority or all of their nutritional support from these products.

The October 24, 2011 petition for inclusion of L-methionine in infant formulas based on soy protein submitted by the International Formula Council (IFC) led to the recommendation for L-methionine in soy-based infant formula's inclusion on the National List by the National Organic Standards Board at its October, 2012 meeting. The IFC petition provided the necessary information on L-methionine required by the National Organic Program. We are using some of the information in this comprehensive and factual IFC petition to further support our petition in conjunction with our information on the need for L-methionine in nutritionally complete pediatric enteral products for children. Our petition and attachments provide the necessary information as required in the current Guidelines on Procedures for Submitting National List Petitions and satisfy the criteria in the OFPA.

Please contact us to provide any additional information if required to proceed with the review process and recommendation from the National Organic Standards Board.

Sincerely,

Jay Highman, President
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Lewis Center, OH 43055
Telephone: 740-548-0135
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http://www.hipaaspace.com/Medical_Billing/Coding/Healthcare.Common.Procedure.Coding.System/B4159 Sourced: March 28, 2016

Petition for Inclusion of L-Methionine on the National List for Use In Nutritionally Complete Pediatric Enteral Formula Based on Soy Protein

Item A

The petitioned substance L-methionine will be included on § 205.605, non-agricultural (non-organic) substances allowed in or on processed products labeled as "organic" or "mad with organic (specified ingredients)," with the annotation "for use only in infant formula and nutritionally complete pediatric enteral formula based on soy protein."

Item B

1. The substance's chemical or material common name.

The name of the substance is L-methionine. L-methionine is an essential amino acid for humans. Amino acids are the building blocks of protein. An essential amino acid is one that must be provided in foods from one's daily diet since the human body does not have the capability of producing it for normal growth and development of a young child.

Synonyms for L-methionine include the following:

(S)-2-Amino-4-(methylthio)butanoic acid 2-
Amino-4-(methylthio)butyric acid, (s)-2-
Amino-4-methylthiobutanoic acid (S)-
Butanoic acid, 2-amino-4-(methylthio)-, (S)-
L(-)-Amino-gamma-methylthiobutyric acid
L-alpha-Amino-gamma-methylmercaptobutyric acid
L-alpha-Amino-gamma-methylthibutyric acid L-
Gamma-Methylthio-alpha-aminobutyric acid

The form of L-methionine used in human nutrition must be the natural "L-form," the physiologically occurring form of methionine. Use of the natural "D-form" is prohibited by the FAO/WHO Codex Alimentarius Commission Standard for follow-up formula, a form of nutritionally complete pediatric enteral formula, as noted in Appendix A.

2. The manufacturer's or producer's name, address and telephone number and other contact information of the manufacturer/producer of the substance listed in the petition.

The manufacturer currently certified as the supplier of L-methionine is Evonik-Rexim Pharmaceutical Company, a Division of Evonik Industries AG in Essen, Germany.

Evonik Rexim (Nanning) Pharmaceutical Co., Ltd
No. 10, Wenjiang Road
Wuming County
530100 Nanning, China

c/o Evonik Degussa Corp. USA
299 Jefferson Road
Parsippany, NJ 07054
Tel.: 973-929-8000
Fax.: 973-929-8013

3. The current use of L-methionine is as a nutritionally essential amino acid used to improve the biological value of infant formula and nutritionally complete pediatric enteral formula based on soy protein.

The current use of L-methionine is as a nutritionally essential amino acid used to improve the biological value of infant formula and nutritionally complete pediatric enteral formula based on soy protein used in medical nutrition therapy (MNT). Products labeled as a toddler formula, also known as follow-up formula, are used as nutritionally complete pediatric enteral formulas in situations where a child age 1 to 3 years of age is in need of MNT due to medical, nutritional, physical and/or psychological conditions affecting feeding and nutritional status.

The definition of "enteral nutrition" is:

> "Enteral nutrition (EN) is nourishment administered into the gastrointestinal tract, either orally or through a feeding tube."[1]

The definition of "Medical Nutrition Therapy" is:

> "Medical Nutrition Therapy (MNT) is an evidence-based application of the Nutrition Care Process. The provision of MNT (to a patient/client) may include one or more of the following: nutrition assessment/re-assessment, nutrition diagnosis, nutrition intervention and nutrition monitoring and evaluation that typically results in the prevention, delay or management of diseases and/or conditions."[2]

Unlike soy-based infant formulas that must meet the U.S. Food and Drug Administration (FDA) regulation [21 CFR 107.100(f)] requiring the addition of L-methionine to satisfy the protein biological value, nutritionally complete pediatric enteral formulas, regardless of protein source, have no nutrient specific FDA requirements. However, a sister agency to FDA within the U.S. Department of Health and Human Services, the Centers for Medicaid and Medicare, has defined nutritionally complete pediatric enteral formulas through the Healthcare Common Procedure Coding System (HCPCS). This system is a set of health care procedure codes necessary for Medicare, Medicaid, and other health insurance programs for identification of products allowed and for payment of medical claims. With the implementation of the Health Insurance Portability and Accountability Act of 1996 (HIPAA), use of HCPCS codes for transactions involving health care information is mandatory. B codes are used for enteral (by oral or tube feedings) and parenteral (intravenous) nutrition therapy.

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[1] Corkins, MR, (editor-in-chief). The A.S.P.E.N Pediatric Nutrition Support Core Curriculum, 2nd edition, Silver Springs, Maryland: American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.), 2015: page 185.

[2] Academy of Nutrition and Dietetics. Definition of Terms List. Chicago, Illinois: Academy of Nutrition and Dietetics, January, 2016: page 25.

The code HCPCS B4159 has been assigned to nutritionally complete pediatric enteral formulas based on soy protein. (Appendix A) The definition for HCPCS B4159 is:

> "Enteral formula, for pediatrics, nutritionally complete soy based with intact proteins, including proteins, fats, carbohydrates, vitamins and minerals, may include fiber and/or iron, administered through an enteral feeding tube, 100 calories = 1 unit."[3]

Many state insurance plans have expanded this definition of enteral nutrition to include nutritional support by oral feeding as well as enteral tube feeding.[4,5]

In addition, the FAO/WHO Codex Alimentarius Commission created a Codex Standard for "follow-up formula" (CODEX STAN 156-1987). In the United States, the term "toddler formula" is used and meets the definition of the Codex Standard. "Follow-up formula" and "toddler formula" also meet the definition for nutritionally complete pediatric enteral formula as defined by the B codes of the Centers for Medicare and Medicaid. The following definitions are from the Codex Alimentarius Standard 156-1987 as shown in Appendix B:

> ***Follow-up formula*** is a food prepared from the milk of cows or other animals and/or other constituents of animal and/or plant origin, which have been proved to be suitable for infants from the 6th month on and for young children. (Section 2.2)
>
> The term ***Young children*** means persons from the age of more than 12 months up to the age of three years (36 months). (Setion 2.1.3)

The Codex standard requires a minimum biological quality of the protein in follow-up formula and also requires the L-form of an amino acid, including methionine.

The Committee on Nutrition of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition) specifically set a minimum L-methionine level of 29 mg/100 kcal for follow-up formula based on soy protein as shown in Appendix C. The addition of L-methionine to soy-based nutritionally complete pediatric enteral formulas is just as critical to young children as it is to infants, especially those who must receive all of their nutritional support from these formulas.

4. L-methionine is currently used as an ingredient in infant formulas and nutritionally complete pediatric enteral formulas based on soy protein.

Soy protein contains sufficiently less of the essential amino acid methionine than do the proteins in human milk, cow's milk and goat's milk resulting in methionine becoming the "limiting essential amino

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[3] http://www.hipaaspace.com/Medical_Billing/Coding/Healthcare.Common.Procedure.Coding.System/B4159 Sourced: March 28, 2016

[4] http://www.hca.wa.gov/medicaid/billing/documents/guides/enteral_nutrition_bi.pdf Sourced: March 29, 2016

[5] http://www.mass.gov/eohhs/docs/masshealth/guidelines/mg-enteralnutrition.pdf Sourced: March 29, 2016

acid" (the essential amino acid in lowest relative amount for adequate growth and development) of soy protein. Supplementing soy protein based formulas with L-methionine improves the biological value of the protein and makes it nutritionally complete and equivalent to breast milk, cow's milk-based infant formulas, and cow's milk-based nutritionally complete pediatric formulas in its ability to sustain normal growth and development of infants and young children.

5. The source of the substance and a detailed description of its manufacturing or processing procedures from the basic component(s) to the final product.

The following information is excerpted and adapted from the description of L-methionine in the Hazardous Substances Data Base prepared by the National Library of Medicine and taken from an authoritative and reliable source.[6]

The production method of choice for L-methionine is the enzymatic resolution of racemic N-acetyl-DL methionine using acylase from Aspergillus oryzae. The production is carried out in a continuously operated fixed-bed or enzyme membrane reactor. Alternatively, L-methionine may be produced by microbial conversion (fermentation) of the corresponding 5-substituted hydantoin. Growing cells of Pseudomonas sp. Strain NS671 convert DL- 5-(2-methylthioethyl) hydantoin to L-methionine; a final concentration of 34 g/L and a molar yield of 93% have been obtained.

Supplier Evonik Rexim uses an enzymatic process in the production of L-methionine.

6. A summary of any available previous reviews by State of private certification programs or other organizations of the petitioned substance.

On January 31, 2015, the Livestock Subcommittee of the National Organic Standards Board approved the following revised motion:

> "DL-methionine, DL-methionine-hydroxy analog, and DL-methionine-hydroxy analog calcium (CAS #'s 59-51-8, 583-91-5, 4857-44-7, and 922-50-9) – for use only in organic poultry Production at the following maximum average pounds per ton of 100% synthetic methionine in the diet over the life of the flock: Laying chickens – 2 pounds; Broiler chickens – 2.5 pounds; Turkeys and all other poultry – 3 pounds."

Of note, the sources of methionine approved in this motion for poultry include the DL-form and two synthetic analogs of methionine, all of which are NOT allowed in infant formula and are also not appropriate for nutritionally complete pediatric enteral formulas made with soy protein.

The L-form of methionine has been petitioned, formally reviewed by the National Organic Standards Board, and has been recommended for us in organic handling of infant formula based on soy protein.

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[6] Eggersdorfer M, et al. Ullmann's Encyclopedia of Industrial Chemistry, 7th edition. New York, New York: John Wiley & Sons, 2008

The complete and most current report on L-methionine (CASRN: 63-68-3) in the National Library of Medicine's Hazardous Substances Data Bank can be found at the Toxicology Data Network (TOXNET) website: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~wIHLTh:3
(Note: this website requires use of the "Search" feature and L-methionine must be typed into the Search field for the complete, updated report)

7. Regulatory Information

The FDA regulates the use in foods of amino acids including L-methionine, at 21 CFR 172.320 as shown in Appendix D. L-methionine is a food additive permitted for direct addition to food for human consumption as long as: 1) the quantity of the substance added to food does not exceed the amount reasonably required to accomplish its intended physical, nutritive, or other technical effect in food, and 2) any substance intended for use in or on food is appropriate food grade and is prepared and handled as a food ingredient.

The FDA promulgates the infant formula regulations under the authority of the Infant Formula Act. This Act, 21 CFR 107.100(f) requires a minimum biological quality for the protein in infant formula. The addition of L-methionine to infant formula based on soy protein is required for normal growth and development of an infant and to also achieve the minimum biological quality required at 21 CFR 107.100(f). However, there are no such nutrient specific regulations promulgated by the FDA at present for a formula designed for use in children 1 to 3 years of age (toddler formula) or for toddler formulas used as nutritionally complete pediatric enteral formulas unless these enteral formulas are clearly labeled for a specific medical disorder, disease, or condition for which there are specific nutrition requirements and, hence, are considered medical foods as defined by statute under 21 U.S.C. 360ee(b)(3). The nutritionally complete pediatric enteral formulas made with soy protein covered in this petition are not a medical food and are not regulated by the FDA as a medical food.

Nutritionally complete pediatric enteral formula is also not considered a dietary supplement by the FDA and this can be readily noted by the fact that such formulas are labeled with a Nutrition Facts panel rather than a Supplement Facts panel. Nutritionally complete pediatric enteral formulas that are not disease specific, including toddler formulas, are regulated by the FDA as conventional foods and follow all FDA guidance on label content.

8(a) The Chemical Abstract Service (CAS) number of L-methionine is 63-68-3.

8(b) The label information of currently marketed nutritionally complete pediatric enteral formulas made with soy protein that contain L-methionine are shown in Appendix E.

9. The substance's physical properties and chemical mode of action.

Physical Properties:

Physical state and properties:	Powdered solid
Color:	White
Odor:	Slight
Taste:	Sulfurous
Molecular Weight:	149.21 g/mole
Solubility:	Soluble in water, warm dilute alcohol
pH (1% solution in water):	5.85 (slightly acidic)
Melting Point:	281° C (537.8° F)

Mode of Action: L-methionine is an essential amino acid. Humans cannot fix inorganic sulfur into organic molecules and must rely on ingested sulfur amino acids, such as methionine, for the synthesis of protein and biologically active sulfur.

L-methionine is currently used as a nutritionally essential amino acid needed to improve the biological value of marketed organic and inorganic infant formula and nutritionally complete pediatric enteral formula based on soy protein. L-methionine has been added to conventional soy-based infant formula in the United States for almost 50 years.

9(a) Chemical interactions with other substances, especially substances used in organic production.

L-methionine has been recommended by the National Organic Standards Board for inclusion on the National List for use in soy-based organic infant formula. L-methionine is an unreactive powder that easily blends into dry mixes and is soluble in water, especially warm or hot water, so it can be dispersed in wet mashes. DL-methionine is allowed on the National List for use in poultry rations to improve the quality of plant-based rations.

9(b) Toxicity and environmental persistence (Source of data: Hazardous Substances Data Bank found at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~wlHLTh:3)

Human toxicity: Based on distribution data from the 1984-1994 NHANES III, the mean daily intake for all life stage and gender groups of methionine from food supplements is 1.8 grams per day. Men 51 through 70 years of age had the highest intakes at the 99th percentile of 4.1 grams per day.[7]

Methionine supplements (5 gm/day) for periods of weeks were reportedly innocuous in humans. Single oral doses of 7 grams produced lethargy in 6 individuals and oral administration of 10.5 grams of L-methionine to one person produced nausea and vomiting.

Non-Human Toxicity: Methionine is an essential amino acid for rats, mice, poultry, swine, as well as for humans. L-methionine needs to be furnished along with other essential amino acids in humans for it to be incorporated into the proteins needed for normal growth and development. A diet devoid of

[7] Institute of Medicine. *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* Washington, DC: National Academies Press, 2005: page 725.

methionine does not sustain life. Conversely, administering a large, non-physiological level of L-methionine, in the absence of other essential amino acids, can create metabolic imbalance and toxicity.

A single dietary dose (2.7% of the diet) of L-methionine decreased body growth and also reduced food intake in rats. Dietary excesses of L-methionine (2.7% of the diet) for 6, 13, or 20 days have been associated with erythrocyte engorgement and accumulation of hemosiderine in rats, and there was a depression of growth and splenic damage. Dietary intakes of 2 to 4% of L-methionine caused slight changes in liver cells in rats and slight decreases in liver iron content. Darkened spleens caused by increases in iron deposition have been observed in weanling rats fed 1.8% methionine diets for 28 days. Male Wistar rats were fed either an L-methionine-supplemented (2.5 g/100 g) diet without changing any other dietary components or a control (0.86 g/100 g) diet for 7 weeks. L-methionine supplementation in the diet specifically increases mitochondrial ROS production and mitochondrial DNA oxidative damage in rat liver mitochondria offering a plausible mechanism for its hepatoxicity.

Environmental Persistence: L-methionine is formed in natural waters through metabolism of naturally occurring proteins. It is one of the nine indispensable amino acids that cannot be synthesized to meet human body needs in animals and therefore must be provided in the diet. L-methionine is not expected to adsorb to suspended solids and sediment. The potential for bioconcentration in aquatic organisms is low. Using a laboratory activated sludge system, L-methionine exhibited an 80% theoretical BOD reduction in 16 days.

L-methionine has been shown to degrade in sunlit natural water through a photo-sensitized oxidation involving singlet oxygen. Assuming that the top meter of sunlit natural water has a singlet oxygen concentration of 4X10-14 M, the photo oxidation half-life for the reaction L-methionine with singlet oxygen has been estimated to be about 200 hr at pH 6-11. The near-surface photo oxidation rate (via singlet oxygen) of L-methionine in Okefenokee Swamp water from Georgia is predicted to be about 3 hr. Bioconcentration and volatilization are not expected to be important fate processes because of its high water solubility.

(c) Environmental impacts from its use and/or manufacture.

L-methionine is an essential amino acid that cannot be synthesized in the human body and must therefore be provided in the daily diet. L-methionine is used in normal metabolism and is incorporated into the protein of every living organism on the earth. It is rapidly biologically degraded in aquatic systems.

In 2011, the environmental impact of the use and manufacture of synthetic methionine was described in correspondence from Degussa (predecessor to Evonik) to the National Organic Program and this is available as Appendix B of the International Formula Council's petition for inclusion of L-methionine in infant formula made with soy protein and can be found on the National Organic Program's website at https://www.ams.usda.gov/sites/default/files/media/Methionine%20%28L-Methionine%29.pdf

The manufacturing plant of Evonik Rexim is ISO-certified and FDA-inspected and operates according to HAACP (Hazard Analysis/Critical Control Points) requirements. Sustainable development is an integral part of the business process. Economic, ecologic, and societal aspects are given equal consideration.

(d) Effects on human health.

L-methionine is an essential, indispensable amino acid. Humans cannot fix inorganic sulfur into organic molecules and must rely on ingested sulfur amino acids, such as methionine, for the synthesis of protein and biologically active sulfur compounds.

L-methionine has other, non-nutritional uses. It is used as a hepatoprotectant (liver protector) and as an antidote to acetaminophen poisoning, the result of which is liver damage.

(e) Effects on soil organisms, crops, or livestock.

Poultry have a greater need for this essential sulfur-containing amino acid than do other food and fiber livestock sources because they have feathers. DL-methionine is a customary ingredient in poultry rations. L-methionine can replace the DL-form in this application.

On January 31, 2015, the Livestock Subcommittee of the National Organic Standards Board approved the following revised motion:

> "DL-methionine, DL-methionine-hydroxy analog, and DL-methionine-hydroxy analog calcium (CAS #'s 59-51-8, 583-91-5, 4857-44-7, and 922-50-9) – for use only in organic poultry Production at the following maximum average pounds per ton of 100% synthetic methionine in the diet over the life of the flock: Laying chickens – 2 pounds; Broiler chickens – 2.5 pounds; Turkeys and all other poultry – 3 pounds."

10. Safety information about the substance including a Material Safety Data Sheet (MSDS) and a substance report from the National Institute of Environmental Health Studies.

An MSDS for 2011 from Evonik Industries submitted with the International Formula Council's petition for L-methionine in soy-based infant formula continues to be applicable and is shown in Appendix F. The Hazardous Substances Data Bank information for L-methionine prepared by the National Library of Medicine is found at
http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~vf5R2n:3

11. Research information about L-methionine, including comprehensive substance research reviews and research bibliographies.

General nutritional research information for L-methionine has been summarized by the Institute of Medicine in the publication *Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids.* National Academies Press, 2005, and is included in Appendix G.

This petition requests the allowance on the National List of L-methionine not only for use in soy-based infant formula but also in soy-based nutritionally complete pediatric enteral formula. This section of the petition focuses on research information about this use.

The commercial definition of "protein isolate" is a material with no less than 90% protein, dry matter basis. Conventional soy protein isolate is produced from hexane-extracted soy flakes and the acidifier is

hydrochloric acid; both hexane and hydrochloric acid are unacceptable in an organic process. One commercial process (U.S. Patent Application 20070207255, published September 6, 2007: "Plant-derived protein compositions.") for organic soy protein isolate uses carbon dioxide to "de-fat" full fat soy flour and citric acid for pH adjustment. Because mechanical pressing is not as efficient a means for removing soy oil from soybeans as is hexane extraction, the soy protein material resulting from this organic process contains about 15% oil and thus less than 90% protein and it cannot be designated "soy protein isolate" but is instead called isolated soy protein. Isolated soy proteins have substantially identical amino acid profiles, confirming that they contain the same globular protein fraction of the soybean.

Organic soy protein concentrate is a variation of organic isolated soy protein. A proprietary mechanical process to produce soy protein products without the use of solvents or other chemicals was developed by Harvest Innovations. The process is to condition organic soybeans through an extrusion treatment to impart some heat and open the cell structure of the soybean followed by extracting the soy oil be expeller pressing. Protein functionality of these products has been shown to be similar to that of conventional soy protein isolates. Harvest Innovations has named these products under the trade name "HIsolate®" to distinguish them from conventional soy protein isolates. Organic soy protein concentrate has substantially the same amino acid profile as conventional soy protein isolates and the protein chemistry remains the same. Hence, HIsolate® organic soy protein concentrate is used as an alternative to conventional soy protein isolates and organic isolated soy protein.

The nutritional research conducted on conventional soy protein isolates published over the past 50 years is applicable to organic isolated soy protein and organic soy protein concentrate.

Since the late 1970s, clinical research has supported the addition of L-methionine to soy-based infant formula. The clinical research has been presented to the National Organic Standards Board and the National Organic Program through the International Formula Council's petition for inclusion of L-methionine on the National List for use in infant formula based on soy protein as found at https://www.ams.usda.gov/sites/default/files/media/Methionine%20%28L-Methionine%29.pdf We refer to this document for the research on L-methionine in pediatric formulas.

Federal regulation 21 CFR 107.100(f) requires that the protein efficiency ratio (PER) of the nitrogen source of an infant formula be at least 70% of that of casein, a standard milk-based protein. Isolated soy proteins used in infant formula are supplemented with L-methionine, the limiting amino acid. The extent of supplementation is that necessary to meet the requirement of the FDA regulation with respect to PER. There are no such FDA regulations for nutritionally complete pediatric enteral formulas, regardless if they are labeled as "toddler formula" or "follow-on formula." However, the need for L-methionine supplementation in these formulas designed for young children is just as great, especially when they are used as a sole-source of nutrition when food is not an option.

A major authoritative body, the Committee on Nutrition of ESPGHAN (European Society of Pediatric Gastroenterology, Hepatology and Nutrition), reviewed soy-based infant and follow-on formulas twice in the past 25 years. These two reviews are shown as Appendix C and Appendix H.

In 1990, the ESPGHAN statement was:

> "Isolated soy protein if appropriately processed is a good vegetable protein source for children. It has a high nutritional value and its amino acid composition rating is 96% that of casein, and

> even after allowance has been made for digestibility, the amino acid score is 89% overall and still remains above 80% when the least available amino acid, methionine, is considered, but nevertheless this is limiting. Thus even when protein intake is not marginal, methionine supplements are needed to ensure growth, and to maintain nitrogen balance and circulating plasma albumin concentrations. The Committee considers, therefore, that soy protein isolate based infant and follow-on formulas should contain at least 30 mg (200 pmol) of methionine/100 kcal (50 pmol (7.3 mg)/100 kJ, approximating the normal amount in human breast milk."

In 2006, the Committee on Nutrition of ESPGHAN wrote:

> "Soy protein isolates are derived from delipidated soy flour (90-95%) by elimination of soluble carbohydrates and mineral salts. Soy protein has a lower biologic value than cows' milk protein. The nitrogen conversion factor, which allows us to calculate the protein content from the total nitrogen content, is lower for soy protein isolate than cows' milk protein. Soy and cows' milk proteins have a different amino acid pattern (i.e., soy protein contains lower amounts of methionine, branched chain amino acids, lysine, and proline and higher quantities of aspartate, glycine, arginine, an cysteine than cows' milk proteins.) To ensure adequate growth, nitrogen balance, and plasma albumin concentrations, methionine supplements have been recommended."

The Committee specifically set a minimum L-methionine level of 29 mg/100kcal for follow-on formula based on soy protein.

12. Petition Justification Statement for Inclusion of Synthetic L-Methionine on the National List at §205.605(b)

Methionine has an important role in the functioning of the body.

- Methionine is a source of sulfur for various liver functions including detoxification.
- Methionine is important in the synthesis of many amino acids including cysteine.
- Methionine is converted into S-adenosylmethionine (SAMe), an active form of methionine used by the body to manufacture many brain chemicals and used in detoxification reactions.
- Methionine is a lipotropic factor involved in fat metabolism.

A deficiency of methionine can cause liver dysfunction and lead to a fatty liver, toxic elevation of metabolic waste products, slow growth, edema, skin lesions, and brittle hair.

L-methionine needs to be added to nutritionally complete pediatric enteral formula based on soy protein to satisfy the protein biological value needed to support normal growth and development of young children 1 to 3 years of age. Only the L-form of methionine is appropriate for infant and nutritionally complete pediatric enteral formulas. L-methionine is necessary for the production of an organic soy-based nutritionally complete pediatric enteral formula. Currently, all commercially available L-methionine is made from synthetic intermediates, followed by a final fermentation or by enzymatic resolutions and would thus meet the definition of a synthetic as per §205.2. There are no other alternatives at present for L-methionine supplementation of these formulas.

Soy-based nutritionally complete pediatric enteral formulas may be indicated in the following situations:

- Lactose intolerance or hereditary lactase deficiency
- Children with galactosemia (a genetic disorder treated by dietary exclusion of all dairy and lactose containing products)
- Children whose families prefer a vegetarian diet
- Children with intolerance to cows' milk protein

A soy-based nutritionally complete pediatric enteral formula is recommended by a healthcare professional as either supplemental nutrition or as a total source of nutrition depending upon the child's medical and nutritional status. The Centers for Medicare and Medicaid have assigned the Healthcare Common Procedure Coding System code HCPCS B4159 for soy-based nutritionally complete pediatric enteral formula. This code is used by federal, state and private insurance companies to identify products that are allowed and under what conditions for reimbursement of medical claims.

13. A Confidential Business Information Statement.

This petition contains no Confidential Business Information.

Appendix A

Medicare Pricing, Data Analysis and Coding

Jump to content

noridian
Healthcare Solutions
Noridian Healthcare Solutions, LLC

PDAC
Medicare Pricing, Data Analysis and Coding

Mission Statement: Pricing, Data Analysis and Coding (PDAC) contractor is committed to quality and accurate results, within time frames that exceed our customers' expectations and is of great value to CMS.

PRODUCT SEARCH RESULTS

Your search for
Classification:
HCPCS Code: B4159
Manufacturer/Distributor:
Product Name:
Model Number:

Returned 30 results

This list reflects products which have been submitted by the manufacturer for a HCPCS coding verification review. The assignment of a HCPCS code to the product(s) should in no way be construed as an approval or endorsement of the product(s) by the PDAC, DME MACs, or Medicare, nor does it imply or guarantee claim reimbursement. This list reflects the latest product information on file, therefore, the information displayed in the results table may differ from the search criteria you entered for manufacturer name, product name, and model number.

First Prev Next Last | 100 Rows Displayed

30 results found, displaying 1 to 30

Product Name	Manufacturer/Distributor	Model Number	HCPCS Code	Effective Begin Date	Effective End Date	Comments
A-SOY	PBM PRODUCTS LLC		B4150 OR B4159	03/26/2008		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
BABY'S CHOICE SOY WITH IRON WITH LIPIDS DHA & ARA	PBM PRODUCTS LLC		B4159	07/13/2007		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
BABY'S ONLY ORGANIC PARVE SOY TODDLER FORMULA	NATURE'S ONE INC	53952	B4159	10/28/2014		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
BABY'S ONLY ORGANIC SOY TODDLER FORMULA	NATURE'S ONE INC		B4159	01/01/2009		
ENFAGROW SOY TODDLER INFANT AND TODDLER FORMULA 24 OZ POWDER CAN	MEAD JOHNSON & COMPANY LLC	UPC:0030087-14094-46	B4159	10/09/2012		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
ENFAGROW SOY TODDLER SOY MILK DRINK POWDER	MEAD JOHNSON & COMPANY LLC	NDC: 0087-1409-45	B4159	08/26/2011		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
ENFAMIL NEXT STEP PROSOBEE LIPIL	MEAD JOHNSON & COMPANY LLC		B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
ENFAMIL PROSOBEE	MEAD JOHNSON & COMPANY LLC		B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
ENFAMIL PROSOBEE 8 FL OZ BOTTLE CONCENTRATE	MEAD JOHNSON & COMPANY LLC	UPC: 0087-5102-52	B4159	04/11/2012		
ENFAMIL PROSOBEE 8 FL OZ BOTTLE RTU	MEAD JOHNSON & COMPANY LLC	UPC: 0087-5102-50	B4159	04/11/2012		

ENFAMIL PROSOBEE LIPIL	MEAD JOHNSON & COMPANY LLC	B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
GERBER GOOD START 2 SOY	NESTLE INFANT NUTRITION	B4159	05/02/2012		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
GERBER GOOD START SOY	NESTLE INFANT NUTRITION	B4159	04/30/2012		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
GERBER GRADUATES SOY - 24OZ CAN (POWDER)	NESTLE INFANT NUTRITION	B4159	06/20/2014		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
GOOD START 2 SOY ESSENTIALS WITH IRON	NESTLE HEALTHCARE NUTRITION INC	B4159	01/01/2005	04/30/2012	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.MANUFACTURER DISCONTINUED PRODUCTION AS OF 4/30/2012. BILLING ACCEPTABLE UNTIL EXPIRATION OF PRODUCT.
GOOD START 2 SUPREME SOY DHA & ARA	NESTLE HEALTHCARE NUTRITION INC	B4159	01/06/2006	04/30/2012	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.MANUFACTURER DISCONTINUED PRODUCTION AS OF 4/30/2012. BILLING ACCEPTABLE UNTIL EXPIRATION OF PRODUCT.
GOOD START SOY ESSENTIALS WITH IRON	NESTLE HEALTHCARE NUTRITION INC	B4159	01/01/2005	04/30/2012	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.MANUFACTURER DISCONTINUED PRODUCTION AS OF 4/30/2012. BILLING ACCEPTABLE UNTIL EXPIRATION OF PRODUCT.
GOOD START SUPREME SOY DHA & ARA	NESTLE HEALTHCARE NUTRITION INC	B4159	03/14/2005	04/30/2012	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.MANUFACTURER DISCONTINUED PRODUCTION AS OF 4/30/2012. BILLING ACCEPTABLE UNTIL EXPIRATION OF PRODUCT.
ISOMIL	ABBOTT NUTRITION	B4159	01/01/2005	10/02/2008	
PARENT'S CHOICE SOY WITH LIPIDS DHA & ARA	PBM PRODUCTS LLC	B4159	07/19/2007		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
PROSOBEE	MEAD JOHNSON & COMPANY LLC	B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC EXPERT CARE FOR DIARRHEA	ABBOTT NUTRITION	B4159	06/30/2011		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC GO & GROW SOY-BASED FORMULA	ABBOTT NUTRITION	B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC ISOMIL ADVANCE SOY FORMULA WITH IRON	ABBOTT NUTRITION	B4159	01/01/2005		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC ISOMIL DF	ABBOTT NUTRITION	B4159	11/02/2005	06/29/2011	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC ISOMIL SOY FORMULA WITH IRON	ABBOTT NUTRITION	B4159	09/19/2005	10/02/2008	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC SENSITIVE ISOMIL SOY	ABBOTT NUTRITION	B4159	08/20/2010	02/07/2011	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
SIMILAC SOY ISOMIL	ABBOTT NUTRITION	B4159	02/08/2011		ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE
	PBM PRODUCTS LLC	B4159	07/31/2007		

TARGET SOY WITH LIPIDS DHA & ARA				ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.
ULTRA BRIGHT BEGINNINGS SOY WITH LIPIDS DHA & ARA	PBM PRODUCTS LLC	B4159	07/19/2007	ADD THE BO MODIFIER TO THE HCPCS CODE IF THE ENTERAL NUTRITION IS BEING ADMINISTERED ORALLY AND IS NOT BEING ADMINISTERED BY A FEEDING TUBE.

Appendix B

Codes Alimentarius Standard For Follow-up Formula CODEX STAN 156-1987

CODEX STANDARD FOR FOLLOW-UP FORMULA
CODEX STAN 156-1987

I. SCOPE

This standard applies to the composition and labelling of follow-up fonnula.

It does not apply to foods covered by the Codex Standard for Infant Fonnula (CODEX STAN 72-1981).

2. DESCRIPTION

2.1 Definitions

2.1.1 *Follow-up formula* means a food intended for use as a liquid part of the weaning diet for the infant from the 6th month on and for young children.

2.1.2 The tenn *infant* means a person of not more than 12 months of age.

2.1.3 The tenn *young children* means persons from the age of more than 12 months up to the age of three years (36 months).

2.1.4 The tenn *calorie* means a kilocalorie (kcal). 1 kilojoule (kJ) is equivalent to 0.239 calories (kcal).

2.2 *Follow-up formula* is a food prepared from the milk of cows or other animals and/or other constituents of animal and/or plant origin, which have been proved to be suitable for infants from the 6th month on and for young children.

2.3 *Follow-up formula* is a food processed by physical means only so as to prevent spoilage and contamination under all nonnal conditions of handling, storage and distribution.

2.4 *Follow-up formula,* when in liquid form, is suitable for use either directly or diluted with water before feeding, as appropriate. In powdered fonn it requires water for preparation. The product shall be nutritionally adequate to contribute to nonnal growth and development when used in accordance with its directions for use.

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS

3.1 Energy Content

When prepared in accordance with the instructions for use, 100 ml of the ready-for-consumption product shall provide not less than 60 kcal (or 250 kJ) and not more than 85 kcal (or 355 kJ).

3.2 Nutrient Content

Follow-up formula shall contain the following nutrients at minimum and maximum levels indicated below:

3.2.1 Protein

3.2.1.1 Not less than 3.0 g per 100 available calories (or 0.7 g per 100 available kilojoules) of protein of nutritional quality equivalent to that of casein or a greater quantity of other protein in inverse proportion to its nutritional quality. The quality [1] of the protein shall not be less than 85% of that of casein. The total quantity of protein shall not be more than 5.5 g per 100 available calories (or 1.3 g per 100 available kilojoules).

3.2.1.2 Essential amino acids may be added to follow-up formula only to improve its nutritional value. Essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L forms of amino acids shall be used.

3.2.2 Fat

3.2.2.1 Not less than 3 g and not more than 6 g per 100 calories (0.7 and 1.4 g per 100 available kilojoules).

3.2.2.2 The level of linoleic acid (in the form of a glyceride) shall not be less than 300 mg per 100 calories (or 71.7 mg per 100 available kilojoules).

3.2.3 Carbohydrates

The product shall contain nutritionally available carbohydrates suitable for the feeding of the older infant and the young child in such quantities as to adjust the product to the energy density in accordance with the requirements set out in Section 3.1.

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[1] Protein quality shall be determined provisionally using the PER method as laid down in the section dealing with methods of analysis.

Vitamins and Minerals

	Amounts per 100 available calories		Amounts per 100 available kilojoules	
	Minimum	Maximum	Minimum	Maximum
324 Vitamins other than Vitamin E				
Vitamin A	250 LU. or 75 µg expressed as retinol	750 LU. or 225 µg expressed as retinol	60 LU. or 18 µg expressed as retinol	180 LU. or 54 µg expressed as retinol
Vitamin D	40 LU. or 1 µg	120 LU. or 3 µg	10 LU. or 0.25 µg	30 LU. or 0.75 µg
Ascorbic Acid (Vitamin C)	8 mg	N.S.[2]	1.9 mg	N.S.[1]
Thiamine (Vitamin B 1)	40 µg	N.S.[1]	IO µg	N.S.[1]
Riboflavin (Vitamin B2)	60 µg	N.S.[1]	14 µg	N.S.[1]
Nicotinamide	250 µg	N.S.[1]	60 µg	N.S.[1]
Vitamin *Bl*	45 µg	N.S.[1]	11 µg	N.S.[1]
Folic acid	4 µg	N.S.[1]	1 µg	N.S.[1]
Pantothenic acid	300 µg	N.S.[1]	70 µg	N.S.[1]
Vitamin B12	0.15 µg	N.S.[1]	0.04 µg	N.S.[1]
Vitamin K 1	4 µg	N.S.[1]	1 µg	N.S.[1]
Biotin (Vitamin H)	1.5 µg	N.S.[1]	0.4 µg	N.S.[1]
325 Vitamin E (a-tocopherol compounds)	0.7 LU.lg linoleic acid[3] but in no case less than 0.7 LU.II00 available calories	N.S.[1]	0.7 LU.lg linoleic acid[4],but in no case less than 0.15 LU./100 available kilojoules	N.S.[1]
326 Minerals				
Sodium (Na)	20 mg	85 mg	5 mg	21 mg
Potassium (K)	80 mg	N.S.[1]	20 mg	N.S.[1]
Chloride (Cl)	55 mg	N.S.[1]	14 mg	N.S.[1]
Calcium (Ca)5	90 mg	N.S.[1]	22 mg	N.S.[1]
Phosphorus (P)6	60 mg	N.S.[2]	14 mg	N.S.[2]
Magnesium (Mg)	6 mg	N.S.[7]	1.4 mg	N.S.[2]

[2] N.S. = Not specified

[3] Fonnulas should contain a minimum of 15 µg Vitamin B_6 per gramme of protein. See Section 3.2.1. 1.

[4] Or per g polyunsaturated fatty acids, expressed as linoleic acid.

[5] The Ca:P ratio shall be not less than 1.0 and not more than 2.0.

[6] The Ca:P ratio shall be not less than 1.0 and not more than 2.0

Iron (Fe)	I mg	2 mg	0.25 mg	0.50 mg
Iodine (I)	5 µg	N.S.[2]	12 µg	N.S.[2]
Zinc (Zn)	0.5 mg	N.S.[2]	0.12 mg	N.S.[2]

3.3 Ingredients

3.3.1 Essential Ingredients

3.3.1.1 Follow-up formula shall be prepared from the milk of cows or of other animals and/or other protein products of animal and/or plant origin which have been proved suitable for infants from the 6th month on and for young children and from other suitable ingredients necessary to achieve the essential composition of the product as set out in Sections 3.1 and 3.2 above.

3.3.1.2 Follow-up formula based on milk shall be prepared from ingredients as set out in Section 3.3.1.1 above except that a minimum of 3 g per 100 available Calories (or 0.7 g per 100 kilojoules) of protein shall be derived from whole or skimmed milk as such, or with minor modification that does not substantially impair the vitamin or mineral content of the milk and which represents a minimum of 90% of the total protein.

3.3.2 Optional Ingredients

3.3.2.1 In addition to the vitamins and minerals listed under 3.2.4 to 3.2.6, other nutrients may be added when required to ensure that the product is suitable to form part of a mixed feeding scheme intended for use from the 6th month on.

3.3.2.2 The usefulness of these nutrients shall be scientifically shown.

3.3.2.3 When any of these nutrients is added, the food shall contain significant amounts of these nutrients, based on the requirements of infants from the 6th month on and young children.

3.4 Purity Requirements

3.4.1 General

All ingredients shall be clean, of good quality, safe and suitable for ingestion by infants from the 6th month on and young children. They shall conform with their normal quality requirements, such as colour, flavour and odour.

[7] N.S. = Not specified

3.4.2 Vitamin Compounds and Mineral Salts

3.4.2.1 Vitamin compounds and mineral salts used in accordance with Sections 3.3.1 and 3.3.2 should be selected from the Advisory Lists for Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children approved by the Codex Alimentarius Commission (CAC/GL 10-1979).

3.4.2.2 The amounts of sodium derived from vitamin and mineral ingredients shall be within the limit for sodium in Section 3.2.6.

35 Consistency and Particle Size

When prepared according to the directions for use, the product shall be free of lumps and of large, coarse particles.

36 Specific Prohibition

The product and its components shall not have been treated by ionizing radiation.

4. FOOD ADDITIVES

The following additives are permitted:

		Maximum Level in 100 ml of Product Ready-for-Consumption
4.1	Thickening Agents	
4.1.1	Guar gum } 0.1 g	
4.1.2	Locust bean gum	
4.1.3	Distarch phosphate	} 0.5 g singly or in
4.1.4	Acetylated distarch phosphate } products only	} combination in soy-based
4.1.5	Phosphated distarch phosphate }	
4.1.6	Acetylated distarch adipate	} 2.5 g singly or in } combination in hydrolyzed } protein and/or amino acid- } based products only
4.1.7	Carrageenan	} 0.03 g singly or in } combination in milk and soy- } based products only } } 0.1 g singly or in } combination in hydrolyzed } protein and/or amino acid- } based liquid products only
4.1.8	Pectins	1 g

		Maximum Level in 100 ml of Product Ready-for-Consumption
4.2	Emulsifiers	
4.2.1	Lecithin	0.5 g
4.2.2	Mono- and Diglycerides	0.4 g
4.3	pH-Adjusting Agents	
4.3.1	Sodium hydrogen carbonate	}
4.3.2	Sodium carbonate	}
4.3.3	Sodium citrate	}
4.3.4	Potassium hydrogen carbonate	}
4.3.5	Potassium carbonate	} Limited by Good
4.3.6	Potassium citrate	} Manufacturing Practice
4.3.7	Sodium hydroxide	} within the limits for sodium in
4.3.8	Potassium hydroxide	} Section 3.2.6
4.3.9	Calcium hydroxide	}
4.3.10	L (+) Lactic acid	}
4.3.11	L (+) Lactic acid producing cultures	}
4.3.12	Citric acid	}
4.4	Antioxidants	
4.4.1	Mixed tocopherols concentrate	} 3 mg singly or in } combination
4.4.2	a-Tocopherol	}
4.4.3	L-Ascorbyl palmitate	} 5 mg singly or in
4.4.4	L-Ascorbic acid and its Na, Ca salts	} combination, expressed as } ascorbic acid (see Section 3.2.6)
4.5	Flavours	
4.5.1	Natural Fruit Extracts	GMP
4.5.2	Vanilla extract	GMP
4.5.3	Ethyl vanillin	5 mg
4.5.4	Vanillin	5 mg
4.6	Carry-Over Principle	

Section 4.1 of the *General Standard/or Food Additives* (CODEX STAN 192-1995) shall apply.

5. CONTAMINANTS

5.1 Pesticide Residues

The product shall be prepared with special care under good manufacturing practices, so that residues of those pesticides which may be required in the production, storage or processing of the raw materials or the finished food ingredient do not remain, or, if technically unavoidable, are reduced to the maximum extent possible.

5.2 Other Contaminants

The product shall be free from residues of hormones and antibiotics, as determined by means of agreed methods of analysis, and practically free from other contaminants, especially pharmacologically active substances.

6. HYGIENE

6.1 To the extent possible in good manufacturing practice, the product shall be free from objectionable matter.

6.2 When tested by appropriate methods of sampling and examination, the product:

(a) shall be free from pathogenic microorganisms;

(b) shall not contain any substances originating from microorganisms in amounts which may represent a hazard to health; and

(c) shall not contain any other poisonous or deleterious substances in amounts which may represent a hazard to health.

6.3 The product shall be prepared, packed and held under sanitary conditions and should comply with the relevant provisions of the *Code of Hygienic Practice for Powdered Formulae for Infants and Young Children* (CAC/RCP 66-2008).

7. PACKAGING

7.1 The product shall be packed in containers which will safeguard the hygienic and other qualities of the food. When in liquid form, the product shall be packed in hermetically sealed containers; nitrogen and carbon dioxide may be used as packing media.

7.2 The containers, including packaging materials, shall be made only of substances which are safe and suitable for their intended uses. Where the Codex Alimentarius Commission has established a standard for any such substance used as packaging materials, that standard shall apply.

8. FILL OF CONTAINERS

In the case of products in ready-to-eat fonn, the fill of container shall be:

(i) not less than 80% v/v for products weighing less than 150 g (5 1/2 oz.);

(ii) not less than 85% v/v for products in the weight range 150-250 g (5 1/2 - 9 oz.); and

(iii) not less than 90% v/v for products weighing more than 250 g (9 oz.)

of the water capacity of the container. The water capacity of the container is the volume of distilled water at 20°C which the sealed container will hold when completely filled.

9. LABELLING

In addition to the requirements of the Codex General Standard for the Labelling of Prepackaged Foods (CODEX STAN 1-1985), the following specific provisions apply:

9.1 The Name of the Food

9.1.1 The name of the food shall be "Follow-up Fonnula". In addition thereto, any appropriate designation may be used in accordance with national usage.

9.1.2 Those products which are prepared from whole or skimmed milk in accordance with Section 3.3.1.2 and where 90% or more of the protein is derived from whole or skimmed milk as such, or with minor modification that does not substantially impair the vitamin and mineral content of the milk, may be labelled "Follow-up Formula based on milk".

9.1.3 All sources of protein shall be clearly shown on the label in close proximity to the name of the food in descending order of proportion by weight.

9.1.4 A product which contains neither milk nor any milk derivative may be labelled "contains no milk or milk products" or an equivalent phrase.

9.2 List of Ingredients

The declaration of the list of ingredients shall be in accordance with Sections 4.2.1, 4.2.2 and 4.2.3 of the Codex General Standard for the Labelling of Prepackaged Foods except that in the case of added vitamins and added minerals, these ingredients shall be arranged as separate groups for vitamins and minerals, respectively, and within these groups the vitamins and minerals need not be listed in descending order of proportion.

9.3 Declaration of Nutritive Value

The declaration of nutrition information shall contain the following information in the following order:

(a) The amount of energy, expressed in Calories (kcal) and/or kilojoules (kJ) per 100 g of the food as sold as well as per specified quantity of the food as suggested for consumption.

(b) The number of grammes of protein, carbohydrate and fat per 100 g of the food as sold as well as per specified quantity of the food as suggested for consumption. In addition, the declaration per 100 calories (or per 100 kilojoules) is pennitted.

(c) The total quantity of each vitamin, mineral and any optional ingredient, as listed in Section 3.3.2 of this standard per 100 g of the food as sold as well as per specified quantity of the food as suggested for consumption. In addition, the declaration per 100 calories (or per 100 kilojoules) is permitted.

9.4 Date Marking and Storage Instructions

In addition to the declaration of date marking and storage instructions in accordance with Sections 4.7.1 and 4.7.2 of the Codex General Standard for the Labelling of Prepackaged Foods, the following provisions apply:

9.4.1 Storage of Opened Food

Storage instructions of opened packages of a food for special dietary uses shall be included on the label if necessary to ensure that the opened product maintains its wholesomeness and nutritive value. A warning should be included on the label if the food is not capable of being stored after opening or is not capable of being stored in the container after opening.

9.5 Information for Util.wttion

9.5.1 Directions as to the preparation and use of the food, and its storage and keeping after the container has been opened shall appear on the label.

9.5.2 The labelling of a Follow-up Fonnula shall include a statement that Follow-up Fonnula shall not be introduced before the 6th month of life.

9.5.3 Infonnation that infants and children fed Follow-up Fonnula shall receive other foods in addition to the food shall appear on the label.

9.6 Additional Requirements

The products covered by this standard are not breast-milk substitutes and shall not be presented as such.

10. METHODS OF ANALYSIS AND SAMPLING

See relevant Codex texts on methods of analysis and sampling.

Appendix C

Medical Position Paper
Soy Protein Infant Formulae and Follow-On Formula:
A Commentary by the ESPGHAN Committee on Nutrition

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Medical Position Paper

Soy Protein Infant Formulae and Follow-On Formulae: A Commentary by the ESPGHAN Committee on Nutrition

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ABSTRACT: This comment by the European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) Committee on Nutrition summarizes available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows• milk protein formulae as well as on their suitability and safety for supporting adequate growth and development in infants. Soy is a source of protein that is inferior to cows' with a lower digestibility and bioavailability as well as a lower methionine content For soy protein infant fonnulae, only protein isolates can be used. and minimum protein content required in the current European Union legislation is higher than that of cows' milk protein infant fonnulae (2.25 g/100 kcal vs. 1.8 g/100 kcal). Soy protein formulae can be used for feeding term infants, but they have no nutritional advantage over cows• milk protein formulae and contain high concentrations of phytate, aluminum, and phytoestrogens (isoflavones). which might have untoward effects. There are no data to support the use of soy protein formulae in preterm infants. Indications for soy protein fonnulae include severe persistent lactose intolerance, galactosemia. and ethical considerations (e.g.• vegan concepts). Soy protein formulae have no role in the prevention of allergic diseases and should not be used in infants with food allergy during the first 6 months of life. If soy protein fonnulae are considered for therapeutic use in food allergy after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge. There is no evidence supporting the use of soy protein formulae for the prevention or management of infantile colic, regurgitation, or prolonged crying. *JPGN 42:352-361, 2006.* Key Words: soy-infant fonnula-follow-on formula-food allergy-phytoestrogens.

INTRODUCTION

Soy formula was first introduced in the United States for feeding young infants in the early 1900s (1). In 1929. soy formula was proposed as a cows• milk substitute for babies with cows' milk intolerance (2). Soy protein formulae are given at some time during the first year of life to approximately 25% of infants in the United States, 13% in New Zealand, 7% in the United Kingdom, 5% in Italy, and 2% in France (3-6).

During the past few years, concerns have been raised over potential risks of soy protein formulae, in particular with regard to high phytoestrogen contents. Authorities or pediatric societies from Australia, Canada, France, Ireland, New Zealand, Switzerland. and the United Kingdom have recently advised health professionals and caregivers that because of concerns raised and limited availability of data, the use of soy protein formulae in infants should be restricted to specific cases (7-9).

The purpose of this comment by the Committee is to review available information on the composition and use of soy protein formulae as substitutes for breastfeeding and cows' milk protein formulae as well as on their suitability and safety for supporting adequate growth and

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development of infants. In preparing this comment, the Committee reviewed expert consensus documents on the use of soy protein formul ae in dietetic products for in fants (5,7-13). Products that do not meet the standards of infan t and follow-on formulae or foods for medical purposes designed for infants, such as soy "mil ks" or juices and fermented soy products, that do not fulfill nutrition al requirements of infants are beyond the scope of this review.

FROM SOYBEANS TO SOY PROTEIN ISOLATE FORMULAE

Soybeans comprise approximately 40% proteins, 35% carbohydrates, 20% fat, and 5% minerals (percent dry weight). Soybean products include oil and soy flour obtained from roasted soybeans ground into a (inc powder. Soy protein isolates are derived from dclipidated soy flour (90-95%) by elimination of soluble carbohydrates and mineral salts (5). Soy prot ein has a lower biologic val ue than cows' milk protein. The nitrogen conversion factor, which allows us to calculate the protei n content from t he total nitrogen content, is lower for soy protein isolate than for cows' milk protein. Soy and cows' mil k proteins have a d ifferent amino acid pallern (i.e., soy protein contains lower amounts of methioni ne, branched chain amino acids lysine, and proli ne and higher quantities of aspartate, glycine, arginine, and cystine than cows' mil k protein) (14). To ensure adequate growth, nitrogen balance, and plasma album in concentrations, methionine supplements have been recommended (15, 16). Because soy based products have a very low content of L-carnitine that may induce low plasma carn itine con- centration s in infants (17), the addition of cam itine to soy formulae has also been recommended (7, 18).

COMPOSITION OF SOY PROTEIN INFANT AND FOLLOW-ON FORM U LAE

Recommendations and Regulations

The ESPGH AN Committee on Nutrit ion publi shed recommendations on the composition of soy protein infant and follow-on form u lae in 1990 (16). Soy protein infant and follow-on formulae marketed in the Eu ropean Union must meet the compositional criteria defined by EU di rectives (19,20). For soy protein infant form u lae, only protein isolates should be used, and the m inimum protein content required by European legislation is higher than t hat of cows' milk protein infant formu lae (2.25 g/ I 00 kcal vs. 1.8 g/100 kcal) to account for potentially lower digestibility and therefore lower bioavailablil ity of soy protein compared with intact cows' m ilk protein. The main differences in compositional criteria between soy protein and cows' milk protein infant formulae, and between soy protein and cows' milk protein follow-on formulae, are listed in Table I .

Nutritiona l Adequacy or Soy Protein Formulae

In the 1970s, Fomon et al. (2 1) studied infants fed, as desired, an infant form u la based on methionine su ppl emented soy protein isolate with a protein content of 1 .64 g/ I 00 kcal and an energy content of 67 kcal/ lOO m L. Infants were fed the formu la exclusively for 28 days and t hereafter combined with complementary feeding until the age of 1 12 days. The infants had a similar growth pallern and sim ilar normal markers of plasma protein metabol ism as breast-fed infants. However, energy in- t akes were sl ightly higher than in infants fed a cows' m i lk fonnu la with a protein content of 1.77 g/ 100 kcal. In a study designed to estimate the requirement of su l fur amino acids of in fants up to the age of 1 12 days, a beneficial effect of L-meth ionine supplementation (7.5 mg/ 100 kcal) on n itrogen balance was only seen with a concomitant soy protein content of 1.8 g/ I 00 kcal. A beneficial effect of methionine supplementation on weight gain or serum concentrntions of urea nitrogen and albumin was only demonstrated at soy protein concentrntions of 2.2 and 2.6 g/ 100 kcal, respectively (22).

Fomon et al. and other invest igators demonstrated that infants exclusively fed methionine-supplemented soy protei n fonnulae during t he first 4 lo 12 months of life showed weight gai n and l inear growth sim i lar to t hat of infants fed con ventional cows' m ilk protei n formulae

TA BLE 1. *Compositional criteria of soy protein isolate il lfal11 and foll ow-onf ormulae.alone or mixed with cows' milk protein, according to the Commission Directive 9 / 1321/ EEC of May 14. 1991 011 il lfal11 f ormulae and f ollow-on for mulae (19)*

	Soy prolcin infanl formulae		Soy protein follow-on formulae	
	Minimum (/J OO kcal)	Maximum (/ 100 kcal)	Minimum (/ IOOkcal)	Maximu m (/ 100 k cal)
Prolein (g)*	2.25	3.0	2.25	4.5
Methionine (mg)	29		29	
L-camitinc (i 1molcs)	7.5			
Lactose (g)t	3.5		1.8	
Iron (mg)	I	2	I	2
Zin c (mg)	0.75	2.4	0.75	

*Soy protein isolate has 10 have a minimal chemical index of at leas!80% in comparison with human milk prolcin for infant fomrnlac and in comparison with human milk or casein for follow-on formulae.

tThere is no minimal contenl for laclose when soy prolcin represenls more ilwn 50% of total protein.

(23,24). Studies were generally less than I year in duration, with exclusive soy protein formula feeding from birth to 4 months. Blood markers of protein metabolism in children fed soy protein formulae were not significantly different from those of infants fed cows' milk formulae. Healthy term infants fed a soy protein formula during their first year of life achieved a bone density similar to breast-fed or cows' milk formula fed infants (25,26). Outcome parameters included serum calcium, magnesium, phosphorus, alkaline phosphatase, parathyroid and 1,25-dihydroxyvitamin D concentrations, and bone mineral content measured with absorptiometry. These data indicate that soy protein formulae can be used for feeding term infants but have no nutritional advantage over cows' milk protein formulae.

In a randomized, controlled study performed in very low birthweight infants from 3 to 8 weeks of age, Hall et al. (27) compared a soy protein infant formula supplemented with calcium, phosphorus, and vitamin D ($n = 17$) with a whey-predominant premature infant formula ($n = 15$). Birth weight (1,206 ± 178 g) and gestational age (30 ± 1.9 weeks) of the soy formula-fed group were not significantly different from the whey formula-fed group (1,143 ± 158 g and 30 ± 1.8 weeks, respectively). The energy content of the whey formula was higher than that of the soy formula (81 kcal/100 mL vs. 67 kcal/100 mL), whereas the protein/energy ratio was identical in both formulae (3 g/100 kcal). The caloric (kcal/kg/day) and protein (g/kg/day) intake was not significantly different between each group because a greater volume of feed was consumed in the soy formula-fed infants. Those fed soy formula had lower weight gain (11.3 ± 2.3 g/kg/day) than infants fed whey-predominant formula (15.3 ± 2.5 g/kg/day) as well as lower protein and albumin blood concentrations. Bone mineralization pattern was the same in both groups. Although no more information is available in this population, the Committee concludes that soy protein formulae should not be used in preterm infants.

Phytate

Soy protein isolate contains some I % to 2% phytate, which may impair the absorption of minerals and trace elements. In experimental animals and in human adults, phytate has a negative effect on intestinal zinc and iron absorption (28). A reduction in phytate contents of soy protein formulae can be achieved by precipitation methods or treatment with phytase. Reduction of the phytate content of soy formula increased the absorption and availability of zinc and copper in infant rhesus monkeys and rat pups and of iron in infants (29,30). Using stable isotope techniques in infants fed a soy protein isolate formula with low contents of phytate (<6 mg/kg liquid formula) or a conventional content (300 mg/kg liquid formula), Davidsson et al. (31) showed that zinc absorption was significantly greater with dephytinized formula (22.6% vs. 16.7%, $P = 0.03$), whereas no significant difference was observed for calcium, iron, copper, and manganese absorption.

Phytate may also interfere with iodine metabolism. Before the supplementation of soy formulae with iodine and the use of isolated soy protein instead of high-fiber soy flour in the mid- I 960s, cases of goiter and hypothyroidism were described in infants fed soy formulae (32,33). The persistence of thyroid insufficiency despite the use of a high dose of levothyroxine has also been observed more recently in infants with congenital hypothyroidism fed soy protein formulae (34,35). A recent study showed that infants with congenital hypothyroidism fed soy protein formulae had a prolonged increase of thyroid stimulating hormone (TSH) when compared with infants fed nonsoy formulae. These infants need close monitoring of free thyroxine and TSH measurements and may need increased levothyroxine doses to achieve normal thyroid function (36). The mechanism of the prolonged increase in TSH blood concentrations is not clear. Malabsorption and increased fecal loss of the supplemented levothyroxine have been shown in animal studies performed before the use of isolated soy protein. Soy protein may also act as a goitrogen. A glycopeptide isolated from soy that blocks iodine uptake and decreases its organification has been described.

Information on the phytate contents of soy protein formulae used in Europe is not publically available. Such information should be disclosed by manufacturers. In view of the considerations discussed above, the Committee strongly recommends that phytate contents in soy protein infant formulae should be effectively reduced, for example, by precipitation methods or phytase treatment.

Nucleotides

The nucleotide content of soy protein formulae is much higher (approximately 310 mg/L) than that of human milk (68-72 mg/L) or cows' milk infant formulae (8-72 mg/L) (37). The Commission Directive 1991/321/EEC has approved the addition of nucleotides to infant and follow-on formulae with a total concentration of up to 5 mg/100 kcal, which is similar to reported data for free ribonucleotides in human milk (approximately 4-6 mg/100 kcal) (19). Because there is no adequate scientific basis at present to conclude that the addition of nucleotides in higher concentrations would provide additional benefits, the Committee discourages the further addition of nucleotides to formulae based on soy protein isolates given their high natural contents.

Aluminum

In 1996, the Committee on Nutrition of the American Academy of Pediatrics (AAP) highlighted the potential risk of aluminum toxicity in infants and children related to the use of soy protein formula contaminated with

aluminum (38). The source of the aluminum is thought to be the aluminum equipment used during the production of soy protein isolates and the nature of mineral salts used in formula production (3). Much higher concentrations of aluminum were found in soy protein formulae (500-2,400 μg/L) than in cow's milk protein formulae (15 μ.g/L) and breast milk (4-65 μg/L). However, daily aluminum intake remained less than 1 mg/kg, which the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives in 1989 considered as the tolerable intake of aluminum (39). Infants fed formulae with the highest contents of aluminum (2.35 mg/L) at the time of the publication would receive an aluminum dose less than 0.5 mg/kg per day at feed intakes up to 200 mL/kg per day. There is inadequate information on the aluminum content of soy protein formulae. Such information should be made available by manufacturers. Although long-term consequences of higher levels of aluminum observed in soy formulae are unknown, continued efforts should be made by manufacturers to reduce the aluminum content of soy protein formula.

Phytoestrogens

Phytoestrogens represent a broad group of plant-derived compounds of nonsteroidal structure that are ubiquitous within the plant kingdom and have weak estrogen activity (9,40). They are present in beans in general and soybeans in particular. Lignanes and isoflavones are the major classes of phytoestrogens of interest from a nutritional and health perspective. The main compounds contained in soy protein-based foods are the isoflavones genistein and daidzein (41). Isoflavones can bind to estrogen receptors, interact with enzyme systems influencing estrogenic activity, and exert weak estrogenic activity (42). It has been suggested that isoflavones may have anticancer properties in animals (43,44) and in human adults (45,46). Isoflavones may contribute to the prevention of cardiovascular disease, breast cancer, osteoporosis, and menopausal disorders (47), and they have been proposed to slow progression of renal disease in adults (48).

Infant formulae based on soy protein isolates contain relatively high concentrations of isoflavones (49). Isoflavone content found in soy formulae commercially available in the United States, United Kingdom, New Zealand, and France ranges from 17.5 to 47 μg/mL and from 123 to 281 μgig of milk powder, with a higher proportion of genistein than of daidzein (8,50-53). Concentrations of isoflavones were much lower in cows' milk and breast milk samples, ranging from 0.1 to 5 μg/L in cows' milk (54) and from 1.6 to 13.6 μ.g/L (U.S.) and from O to 32 μ.g/kg (U.K.) in breast milk, respectively (8,41). Isoflavone content of breast milk varies with mother's diet. Setchell et al. (41) estimated that infants aged 1 to 4 months would receive 6 to 12 mg/kg body-weight per day of total isoflavones, whereas an adult consuming 57 to 85 g of soy-based products may receive 50 to 100mg of total isoflavones (i.e., 0.7 to 1.4 mg/kg/d). Glycosidic conjugates of isoflavones present in soy protdn formulae are hydrolyzed by intestinal glucosidases to their aglucon form, then are absorbed, metabolized in the liver to glucuronide and sulphate conjugates, and subsequently excreted in urine. Short-term studies have shown that no more than 30% of the ingested dose of isoflavones are recovered in urine and feces (41). Knowledge on the bioavailability of isoflavones is still incomplete in young infants (41,52). In 4-month-old infants exclusively fed soy protein isolate formula, Setchell et al. found plasma total isoflavone concentrations ranging from 552 to 1,775 μg/L, with a mean concentration of 980 μg/L. Mean (SD) plasma concentration was 684 (443) μg/L for genistein and 295 (60) μg/L for daidzein. These values were significantly higher ($P < 0.001$) than the mean values for plasma total isoflavone concentrations in infants fed either cows' milk formula (9.4 ± 1.2 μg/L) or breast milk (4.7 ± 1.3 μg/L) (41,50). On a molar basis, isoflavones demonstrated weak estrogenic activity relative to physiologic estrogens, possessing between 1×10^{-4} and 1×10^{-3} of the activity of 17 (3-estradiol (55).

Phytoestrogens given at the high dosage contained in soy-based formulae adversely affected development and neuroendocrine function in different animal species (7,41,56). Isoflavones were found to cause infertility in sheep, known as "clover disease" (57). In utero exposure of rats to high doses of genistein impairs the pituitary secretion of luteinizing hormone (58).

It has been hypothesized that phytoestrogens have the potential to increase thyroid binding globulin (8). Any such increase could transiently increase the binding capacity for thyroxine, thus lowering free thyroxine concentrations. However, there are no data to suggest that phytoestrogens acting by this mechanism produce clinical effects. A retrospective telephone recall epidemiologic study found that children with autoimmune thyroid disease were significantly more likely to have been fed soy formula in infancy (31% vs. 13% in infants without autoimmune thyroid disease) (59). There was no group difference in the frequency and duration of breast feeding. The aglucons of genistein and daidzein were demonstrated to inhibit the activity of thyroid peroxidase purified from porcine thyroid glands when present at concentrations of 1 to 10 μM, resulting in iodinated isoflavone compounds. The presence of at least 150 μM of iodine per liter in the incubation mixture completely protected against the isotlavone-mediated thyroid peroxidase inactivation (60).

Few data are available on the potential consequences of exposure to high doses of phytoestrogens in human infants on the later sexual and reproductive development. A three-fold increase in the number of patients with premature thelarche seen between 1978 and 1981 in Puerto

Rico led to further investigation in a case-control study (61). Onset of thelarche before 2 years of age was significantly associated with consumption of soy protein isolate based infant formula and of various meats. However, less than 20% of cases were soy formula fed, which points to the importance of additional causative factors.

Strom et al. (62) conducted telephone interviews in 811 adults aged 20 to 34 years who had participated as infants during the years 1965 to 1978 in comparative but not randomized feeding trials with soy protein based infant formula (n = 248; 120 males) or cows' milk protein formula (n = 563; 295 males). Outcome measures were self-reported: pubertal maturation, menstrual and reproductive history, height, weight, and education levels. The study did not include any direct measurements of hormone levels. Females previously fed on soy formulae had a lower prevalence of sedentary activities (8.9 ± 3.4 hours/wk vs. 9.6 ± 3.5 hours/wk, $P = 0.05$), whereas there was no difference for males. No statistically significant differences were observed between groups in either men or women for adult height, weight, pubertal development, and incidence of thyroid disease.

Women fed soy formula in infancy experienced a slightly but significantly longer duration of menstrual bleeding (by 0.37 days; 95% confidence interval [CI]: 0.06-0.68), with no difference in self-assessed intensity of menstrual flow. They also reported greater discomfort with menstruation (unadjusted relative risk for extreme discomfort vs no or mild pain, 1.77; 95% CI, 1.04-3.00). Pregnancies were reported by 42% of women fed soy-formulae and 48% of women fed cows' milk formulae (NS). Outcomes of pregnancies were not different, and neither were there differences between the groups in the prevalence of cancer, hormonal disorders, sexual orientation, or birth defects in the offspring. No conclusions can be drawn on possible effects on fertility in men previously exposed to soy-based formulae, considering their relatively young age at the time of the follow-up study. Although exposure to soy formulae in this study did not appear to be responsible for major health or reproductive problems, more information is needed on potential long-term effects of phytoestrogens.

Yellayi et al. (56) showed that subcutaneous genistein injections in ovariectomized adult mice produced dose responsive decreases in thymic weight of up to 80%. Genistein injection caused decreases in relative percentages of thymic CD4+CD8- and double positive CD4+CD8+ thymocytes, providing evidence that genistein may affect early thymocyte maturation and the maturation of CD4+CD8- helper T-cell lineage. Dietary genistein at concentrations that produced serum genistein levels substantially less than those found in soy protein formula-fed infants produced marked thymic atrophy.

In infants fed soy protein formula from birth to 4 months, Ostrom et al. and Cordle et al. (63,64) did not find differences compared with a control group that was breastfed for 2 months or more at 6 and 12 months of age for the level of immunoglobulins (Ig)G and A, the titre of antibodies against diphtheria, tetanus, poliovirus, and *Hemophilus influenzae* b, as well as the count of lymphocytes B, T, and NK. The only significant difference was the higher percentage of CD57+ NK cells in the control group at 12 months.

Information on the phytoestrogen content of soy protein formulae should be made available by manufacturers. Although studies in humans are lacking, on the basis of available data in animal models, the Committee recommends that the content of phytoestrogens in soy protein formulae be reduced because of uncertainties regarding safety in infants and young children.

COMMENTS ON POSSIBLE INDICATIONS FOR SOY FORMULAE

Severe persistent lactose intolerance and galactosemia

Severe persistent lactose intolerance, including severe mucosal damage and the rare cases of hereditary lactase deficiency (McKusick 223000) and classic galactosemia (galactose-1-phosphate uridyltransferase deficiency) (McKusick 230400), are indications for the use of lactose free soy formulae (65). It should be noted that some soy protein formulae contain raffinose and stachyose that are cleaved in the digestive tract under the action of bacterial galactosidases, leading to the liberation of 1,4 galactose that may contribute to elevated galactose-1-P values in erythrocytes of galactosemic patients (66).

Acute gastroenteritis

A meta-analysis of clinical trials on the use of formulae in the management of acute gastroenteritis concluded that lactose-containing diets do not need to be withdrawn in the vast majority of cases, whereas lactose free diets were beneficial in a limited number of cases with severe dehydration (67). An ESPGHAN multicentric study has shown that the early use of lactose containing cows' milk formula after oral rehydration does not aggravate or prolong diarrhea in well-nourished infants presenting with acute gastroenteritis and mild to moderate dehydration and has the advantage of preventing malnutrition (68). Therefore, switching from lactose-containing formula to lactose free formula such as soy formulae is not routinely recommended in acute gastroenteritis (10). Moreover, there are theoretical concerns regarding the introduction of a new protein source in the presence of increased mucosa! permeability, with a potential increased risk of allergic sensitization (69,70).

Cows' milk allergy

Before the availability of therapeutic formulae based on cows' milk protein hydrolysates, soy formula was the only dietetic product available for feeding infants with cows' milk protein allergy. However, soy protein is alsoa common allergen. The identification and characterization of soybean allergens have identified fractions containing conglycinin (molecular weight 180,000 d) and glycinin (molecular weight 320,000 d) as probably the major allergens and trypsin inhibitor as the minor allergen responsible for soy protein allergy (71). Patients with soy protein allergy present with either acute symptoms within a few hours after soy ingestion (i.e., urticaria, angioedema, vomiting, diarrhea, or anaphylactic shock) or with chronic symptoms (i.e. chronic diarrhea and failure to thrive, malabsorption, and villous atrophy) (72,73). Symptoms usually resolve after elimination of soy from the diet.

Among infants with cows' milk allergy fed soy protein based formulae, some 30% to 50% were reported to present with concomitant soy protein allergy, with a higher frequency reported in nonlgE-mediated enterocolitis-enteropathy syndrome (71,74-76). A review of 2,108 infants with cows' milk protein allergy followed at 33 Italian pediatric gastroenterology units reported that 50% of these infants had received soy protein-based formulae as the substitute for milk containing formulae. Soy protein formulae were discontinued in 47% of cases overall, ranging from 53% of infants younger than 3 months of age to 35% of children older than I year of age (4). The reasons for this discontinuation were not given in the publication.

In 1983, the AAP Committee on Nutrition discouraged the use of soy formulae in the dietary management of infants with documented allergy to cows' milk protein (77). The AAP Nutrition Committee concluded in 1998 that infants with documented cows' milk protein-induced enteropathy or enterocolitis are frequently sensitive to soy protein and should not be given soy protein formula routinely, whereas it emphasized that most infants with documented IgE-mediated cows' milk protein allergy will do well when fed soy formula (3). In 1990, the ESPGHAN Committee on Nutrition considered that available data did not support the view that soy formula should be the preferred choice in case of suspected or proven adverse effects to cows' milk protein (16). A joint statement of the ESPGHAN Committee on Nutrition and the European Society for Pediatric Allergology and Clinical Immunology stipulated that, in general, formulae based on intact soy protein isolates are not recommended for the initial treatment of food allergy in infants, although a proportion of infants with cows' milk protein allergy tolerate soy formula (I I). The AAP Nutrition Committee stated in 2000 that infants with IgE-associated symptoms of allergy may benefit from a soy formula, either as the initial treatment or instituted after 6 months of age after use of a therapeutic hydrolysate formula (12).

The exclusion of soy protein from the diet of infants with IgE-mediated cows' milk protein allergy has been a controversial issue for a long time. In 93 children aged 3 to 41 months with IgE-mediated cows' milk protein allergy, Zeiger et al. (78) found a prevalence of concomitant soy allergy of only 14% (Table 2); 3% of the cohort were under 6 months of age at the time of evaluation and challenge. Diagnosis of soy protein allergy in this study was assessed by double-blind, placebo-controlled food challenge response to soy, open challenge response under the direction of a physician, or history of more than one immediate anaphylactic reaction to an isolated ingestion of soy. These investigators regard soy formula as a safe alternative to cows' milk formula for the vast majority of children with IgE-mediated cows' milk allergy, particularly those shown to have negative responses to soy challenge at the time of introduction of soy formula (78).

Klemola et al. (79) recently reported that the presence of concomitant soy allergy in infants with cows' milk allergy is less frequent than previously thought (Table 2). They conducted aprospective, randomized study toevaluate the cumulative incidence of allergy or other adverse reactions to soy formula compared with extensively hydrolyzed formula up to the age of 2 years in infants with

TABLE 2. *Studies on prevalence of soy allergy in immunoglobulin (lg)E-associated cows' milk allergy (CMA) (78) and incidence of allergy to soy formula (SF) and extensively hydrolyzed formula (EHF) in cow' s milk allergy (79)*

Reference	Study design	Allocation concealment	Blinding	Intention-lo-treat analysis	Completeness to follow-up	Participants
Klemola et al., 2002 (79)	RCT	No	Single-blinded	Yes	Yes	n = 170 (with CMA confinned by DBPCFC or history of an anaphylactic reaction)
Zeiger et al., 1999 (78)	Cohort study	NA	NA	NA	NA	n=93, with IgE-medialed CMA

DBPCFC, double-blind, placebo-controlled food challenge; NA, not applicable RCT, randomized clinical trial; RR, relative risk; CI, confidence interval.

confirmed cows' milk allergy. The parents suspected adverse reactions significantly more often in infants randomly assigned to the soy formula than in infants randomly assigned to the extensively hydrolyzed formula (28%; 95% CI 18-39% vs. 11%; 95% CI 5-19%, respectively; relative risk [RR], 2.48; $P = 0.006$). Physicians diagnosed adverse reactions more often with soy than with the extensively hydrolyzed formula (10%; 95% CI 4.4%-18.8% vs. 2.2%; 95% CI 0.3%-7.8%, respectively; RR, 4.50; $P = 0.031$). Adverse reactions to soy were similar in IgE-associated and nonIgE-associated cow's milk allergy (11% and 9%, respectively). Adverse reactions were more common in younger (<6 months) than in older (6 to 12 months) infants (5 of 20 vs. 3 of 60, respectively, $P = 0.01$).

The use of soy formulae may play a role in the etiology of peanut allergy. Evaluating data from the Avon longitudinal study, a geographic-defined cohort study of 13,971 preschool children, Lack et al. (80) showed that peanut allergy was independently associated with intake of soy milk or soy infant formula during the first 2 years of life (odds ratio 2.6; 95% CI 1.4-5.0), suggesting the possibility of cross-sensitization through common epitopes. Soy protein fractions have been shown to be homologous to major peanut proteins (81). It is likely that children with allergy to cows' milk are at increased risk for food allergies, and soy consumption in infancy is increased in response to these atopic disorders. Indeed, a history of allergy to cows' milk (reported prospectively at 6 months) was significantly associated with peanut allergy ($P = 0.03$). In their study assessing the long-term effects of soy protein formulae, Strom et al. (62) showed that, as adults, females who had received soy formula in infancy more frequently used antiallergic and antiasthmatic drugs (18.8% vs. 10.1%, $P = 0.047$), whereas males showed a similar but nonsignificant trend (15.8% vs. 10.2%, $P = 0.08$).

The Committee concludes that for treatment of cows' milk protein allergy, the use of therapeutic formulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein formulae. Given the limited number of infants studied (78,79) and the higher reported rate of adverse reactions to soy protein in infants under 6 months of age (79), the Committee recommends that soy protein formulae should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are used for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.

Prevention of Atopic Disease

The role of soy protein formulae for the prevention of allergic disease in healthy and at-risk infants has been controversial (76,82) and is not supported by evidence from controlled trials (83-87). A recent meta-analysis of five randomized and quasi-randomized clinical trials with appropriate methodology concluded that soy formulae do not prevent food allergy in high-risk infants (13). The joint statement of the European Society for Paediatric Allergology and Clinical Immunology Committee on Hypoallergenic Formulas and the ESPGHAN Committee on Nutrition did not support the use of soy protein formulae for the prevention of allergy in at-risk infants (11).

Infantile Colic and Regurgitation

Soy protein formulae have been widely used in the industrialized countries for symptoms such as infantile colic, regurgitation, or prolonged crying without any convincing evidence for efficacy (23). Controversial data on the use of soy formulae have been obtained in infants with severe infantile colic attributed to cows' milk protein allergy (88,89). One randomized clinical trial showed a mean weekly duration of colic symptoms of 8.7 hours during treatment with soy formula, as compared with 18.8 hours during the control periods (mean difference = 10.1; 95% CI 3.8-16.5) (90). If persisting colic is defined as weeks in which there were 9 or more hours of colic symptoms, then colic persisted in only 31.6% of infants during the soy formula periods as opposed to 94.7% during the control periods (RR 0.33; 95% CI O.ot 7-0.65). The other randomized clinical trial of soy protein formulae did not allow firm conclusions to be drawn because of methodologic drawbacks (91). The meta-analysis of Lucassen et al. (92) collected 27

TABLE 2. *(continued).*

Age (mo)	Intervention group	Control group	Outcomes	Results	RR (95% Cl)
2-11	SF (n = 80)	EHF (n = 90)	Parents suspected adverse reaction to the study fonnula	SF vs. EHF: 28% (95% CI 18-39) vs. 11% (95% CI 5-19)	2.5 (Cl not given)
			DBPCFC confirmed adverse reaction to the study fonnula	SF vs. EHF: 10%; (95% CI 4.4-18.8) vs. 2.2%; (95% 0.3-7.8)	4.5 (1.1-18.4)
3-41	NA	NA	Soy allergy	14% (95% CI 7.7-22.7)	

controlled trials on the effectiveness of diets, drug treatment, and behavioral interventions on infantile colic. Soy protein fonnulae were not effective when only trials of good methodologic quality were considered.

Ethical and Religious Considerations

Some parents (e.g., vegans) seek to avoid cows• milk based fonnulae for their infants for religious, philosophical, or ethical reasons. Soy protein infant fonnulae is an acceptable alternative for these families.

CONCLUSIONS

1. Cows' milk-based fonnulae should be preferred as the first choice for feeding healthy infants that are not fully breast fed.
2. Soy protein based fonnulae should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminum, and phytooestrogens, the long-tenn effects of which are unknown.
3. Indications for soy fonnulae include severe persistent lactose intolerance, galactosemia, religious, ethical, or other considerations that stipulate the avoidance of cows• milk based fonnulae and treatment of some cases of cows' milk protein allergy.
4. The Committee recommends that the use of therapeutic fonnulae based on extensively hydrolyzed proteins (or amino acid preparations if hydrolysates are not tolerated) should be preferred to that of soy protein fonnula in the treatment of cows' milk protein allergy. Soy protein fonnula should not be used in infants with food allergy during the first 6 months of life. If soy protein formulae are considered for therapeutic use after the age of 6 months because of their lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.
5. Soy protein fonnulae have no role in the prevention of allergic diseases.
6. There is no evidence supporting the use of soy protein fonnulae for the prevention or management of infantile colic, regurgitation, or prolonged crying.
7. Manufacturers should aim to reduce the concentrations of trypsin inhibitors, lectins, goitrogenic substances, phytate, aluminum, and phytoestrogens in soy protein fonnulae.

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Appendix D

FDA Regulation §172.320 Amino Acids

be safely used as a component of food, subject to the following restrictions:

(a) The additive is prepared with 50 percent Fischer-Tropsch process synthetic paraffin, meeting the definition and specifications of §172.615, and 50 percent of such synthetic paraffin to which is bonded succinic anhydride and succinic acid derivatives of isopropyl alcohol, polyethylene glycol, and polypropylene glycol. It consists of a mixture of the Fischer-Tropsch process paraffin (alkane), alkyl succinic anhydride, alkyl succinic anhydride isopropyl half ester, dialkyl succinic anhydride polyethylene glycol half ester, and dialkyl succinic anhydride polypropylene glycol half ester, where the alkane (alkyl) has a chain length of 30-70 carbon atoms and the polyethylene and polypropylene glycols have molecular weights of 600 and 260, respectively.

(b) The additive meets the following specifications: Molecular weight, 880-930; melting point, 215°-217 °F; acid number, 43-47; and saponification number, 75-78.

(c) It is used or intended for use as a protective coating or component of protective coatings for fresh grapefruit, lemons, limes, muskmelons, oranges, sweetpotatoes, and tangerines.

(d) It is used in an amount not to exceed that required to produce the intended effect.

§ 172.280 Terpene resin.

The food additive terpene resin may be safely used in accordance with the following prescribed conditions:

(a) The food additive is the beta-pinene polymer obtained by polymerizing terpene hydrocarbons derived from wood. It has a softening point of 112 °118 °C, as determined by ASTM method E28-67 (Reapproved 1982), "Standard Test Method for Softening Point By Ring-and-Ball Apparatus," which is incorporated by reference. Copies may be obtained from the American Society for Testing Materials, 100 Barr Harbor Dr., West Conshohocken, Philadelphia, PA 19428-2959, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741--6030, or go to: *http://www.archives.gov/federal_register/code_of_federal_regulations/ibr_locations.html.*

(b) It is used or intended for use as follows:

(1) As a moisture barrier on soft gelatin capsules in an amount not to exceed 0.07 percent of the weight of the capsule.

(2) As a moisture barrier on powders of ascorbic acid or its salts in an amount not to exceed 7 percent of the weight of the powder.

[42 FR 14491, Mar. 15, 1977, as amended at 49 FR 10104, Mar. 19, 1984]

Subpart 0-Special Dietary and Nutritional Additives

§ 172.310 Aluminum nicotinate.

Aluminum nicotinate may be safely used as a source of niacin in foods for special dietary use. A statement of the concentration of the additive, expressed as niacin, shall appear on the label of the food additive container or on that of any intermediate premix prepared therefrom.

§ 172.315 Nicotinamide-ascorbic acid complex.

Nicotinamide-ascorbic acid complex may be safely used in accordance with the following prescribed conditions:

(a) The additive is the product of the controlled reaction between ascorbic acid and nicotinamide, melting in the range 141°C to 145°C.

(b) It is used as a source of ascorbic acid and nicotinamide in multivitamin preparations.

§ 172.320 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-Gluta.mine
Aminoacetic acid (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), 3d Ed. (1981), which is incorporated by reference (Copies may be obtained from the National Academy Press, 2101Constitution Ave. NW., Washington, DC 20418, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal register/code_of_Jederal _regulations/ibr_locations.html.)* for the following:

L-Alanine
L-Arginine
L-Arginine Monohydrochloride
L-Cysteine Monohydrochloride
L-Cystine
Aminoacetic acid (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 Ed. (1972), which is incorporated by reference (Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http://www.archives.gov/federal register/code_of_federal _regulations/ibr_locations.html.)* for the following:

L-Asparagine
L-Aspartic acid
L-Glutamine
L-Histldine

(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:

(l) A reasonable daily adult intake of the finished food furnishes at least 6.5 grams of naturally occurring primarily intact protein (based upon 10percent 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 Ed. (1968), which is incorporated by reference. Copies are available from the Center for Food Safety and Applied Nutrition (HFS-200), Food and Drug Administration, 5100Paint Branch Pkwy., College Park, MD 20740, or available for inspection at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202-741-6030, or go to: *http:llwww.archives.gov/federal register/code_of_federal_regulations/ibr locations.html.*

(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:

	Percent by weight of total protein (expressed as free amino acid)
L-Alanine	8.1
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
Aminoacetic acid (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	8.4
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 43.212r 43.216, "Official Methods of Analysis of the Association of Official Analytical Chemists," 13th Ed. (1980), which is incorporated by reference. Copies may be obtained from the AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877, or may be examined at the National Archives and Records Administration (NARA). For information on the availability of this material at NARA, call 202r741-6030, or go to: *http://www.archives.gov/federal_register/code_of_Jederal_regulations/ibr locations.html.* 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 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.

(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 105 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.

[42 FR 14491, Mar. 15, 197'1; 42 FR 56'728, Oct. 28, 197'1, as amended at 47 FR 11836, Mar. 19, 1982; 49 FR 10104, Mar. 19, 1984; 54 FR 24897, June 12, 1989; 59 FR 14550, Mar. 29, 1994; 61 FR 14480, Apr. 2, 1996]

§ 172.325 Bakers yeast protein.

Bakers yeast protein may be safely used in food in accordance with the following conditions:

(a) Bakers yeast protein is the insoluble proteinaceous material remaining after the mechanical rupture of yeast cells of *Saccharomyces cerevisiae* and removal of whole cell walls by centrifugation and separation of soluble cellular materials.

(b) The additive meets the following specifications on a dry weight basis:

(1) Zinc salts less than 500 parts per million (ppm) as zinc.

(2) Nucleic acid less than 2 percent.

Appendix E

Label Information – Nutritionally Complete Pediatric Enteral Formulas Made with Soy Protein

R21-P0416
Comp Can
16.9oz Scoop

Nutrition Facts

Serving Size 2 unpacked, level scoops (37.5g) makes 4 fl oz / 120mL prepared
Servings Per Container about 21

Amount Per Serving	1/2c (4 fl oz)	2/3c (5 fl oz)
Calories	80	100
Total Fat	4.5g	5g
Trans Fat	0g	0g
Sodium	25mg	35mg
Potassium	120mg	140mg
Total Carbohydrate	9g	11g
Dietary Fiber	2g	3g
Sugars	4g	5g
Protein	2g	3g
% Daily Value	**4 fl oz**	**5 fl oz**
Protein	10%	20%
Vitamin A	10%	10%
Vitamin C	40%	50%
Calcium	15%	15%
Iron	15%	20%
Vitamin D	10%	20%
Vitamin E	15%	25%
Thiamin (B1)	10%	15%
Riboflavin (B2)	10%	15%
Niacin (B3)	10%	10%
Vitamin B6	8%	10%
Folic Acid (B9)	8%	8%
Vitamin B12	10%	15%
Biotin (B7)	2%	3%
Pantothenic Acid (B5)	6%	8%
Phosphorus	10%	10%
Iodine	10%	10%
Magnesium	6%	10%
Zinc	10%	15%
Copper	8%	8%

Ingredients: Organic Brown Rice Syrup, Organic Soy Protein Concentrate, Organic High Oleic Sunflower and/or Organic High Oleic Safflower Oil, Organic Soybean Oil, Organic Coconut Oil, Calcium Phosphate, Organic Vanilla, Organic Soy Lecithin, Potassium Phosphate, Magnesium Sulfate, Calcium Carbonate, Calcium Ascorbate (Vit. C), Sodium Chloride, Potassium Chloride, Calcium Citrate, Choline Bitartrate, L-Methionine, Taurine, Ferrous Sulfate, Inositol, Zinc Sulfate, d-Alpha Tocopheryl Acetate (Vit. E), L-Carnitine, Niacinamide, Calcium Pantothenate, Vitamin A Palmitate, Thiamin Hydrochloride (Vit. B1), Riboflavin (Vit. B2), Pyridoxine Hydrochloride (Vit. B6), Copper Sulfate, Folic Acid, Phytonadione (Vit. K1), Potassium Iodide, Sodium Selenate, Biotin, Vitamin D3, Cyanocobalamin (Vit. B12).

Contains soy & coconut.

Manufactured for:
NATURE'S ONE®
8754 Cotter Street
Lewis Center, OH 43035

Dairy Free
Gluten Free
Suitable for Lactose Intolerance

Certified Organic by OneCert

For more information:
www.NaturesOne.com
Info@NaturesOne.com
1-888-227-7122

Best when used by date stamped on bottom of can

UPC#
7 16514 53950 8

We Make Organic Better™
Now using organic-compliant technology to help eliminate environmental toxins

Nature's One® recognizes that breast milk is the best source of nutrition a mother can provide her baby. Therefore, Baby's Only Organic® is intended for a toddler 1-year of age and older or as directed by a healthcare professional.

Baby's Only Organic® includes Alpha-Linolenic and Linoleic Fatty Acids the human body converts to DHA & ARA. These fatty acids are found in breast milk and are important for brain and eye development.

Preparation Instructions

Your child's health depends on proper formula preparation. Do NOT exceed recommended water to powder ratio unless specified by a healthcare professional. Failure to follow necessary and these additional dosage instructions could result in poor nutrition and development.

Fill powder to top of enclosed scoop (1 Scoop=8.75g) 1 Can makes about 64 fl oz (2 quarts)

To Make	Water	Add Formula Powder
4 fl oz bottle	2 fl oz (60 mL)	1 unpacked level scoops (8.75g)
8 fl oz bottle	4 fl oz (120mL)	2 unpacked level scoops (17.5g)
12 fl oz bottle	6 fl oz (180 mL)	3 unpacked level scoops (26.25g)
16 fl oz bottle	8 fl oz (240mL)	4 unpacked level scoops (35g)

Pasteurize tap water, then cool to comfortable drinking temperature

Add powder to clean, dry container. Refrigerate unused portion

Cap bottle, shake until powder is dissolved

Warm under hot running water. Shake to mix

Warning: Never use microwave oven to warm formula. Serious burns can result. • Prepared formula must be refrigerated. • Discard leftover formula after feeding. • Powdered formula are not sterile and should not be fed to a child of age 2 and with immune problems unless directed and supervised by a healthcare professional. • The use of water to be purified, demineralized, distilled or reverse osmosis filtered water is not recommended. If using tap water, bring to a rolling boil for one minute and cool before use more than 30 minutes.

Storage: Immediately store prepared formula in refrigerator and discard after 24 hours. • Cover opened formula can and store in original can. Discard any portion left over after 1 month. • Store unopened cans at room temperature, avoid extreme temperatures.

TODDLER FORMULA

Baby's Only ORGANIC®

pure10 pledge®

NON-GMO
SOY
†No Genetically Engineered Ingredients

Parve Ingredients Manufactured on Dairy Equipment

NET WT 12.7 OZ (360g)

Powder Add Water

USDA ORGANIC

Made in the U.S.A.

Mead Johnson Nutrition healthcare professional resource center

"Your Partner in Pediatric Nutrition"

Home

Product Information

Clinical Support

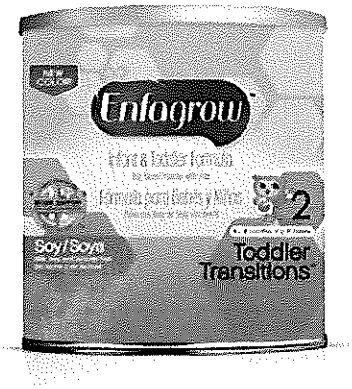
Professional Education

Events

Special Programs

Home > Product Information > Products > Toddlers > Enfagrow Soy Toddler

Please Select One



Enfagrow® Toddler Transitions® Soy

Last Updated: Tuesday, July 7, 2015

Designed for toddlers 9-18 months experiencing fussiness and gas when soy is preferred.

Indication

Product Features

Nutrients†

Nutrient Facts

Product Form

Composition

Ingredients: Powder: Corn syrup solids (58%), vegetable oil (palm olein, soy, coconut and high oleic sunflower oils) (20%), soy protein isolate (17%), calcium phosphate (3%) and less than 1%: *Mortierella alpina* oil‡, *Crypthecodinium cohnii* oil§, vitamin A palmitate, vitamin D_3, vitamin E acetate, vitamin K_1, thiamin hydrochloride, riboflavin, vitamin B_6 hydrochloride, vitamin B_{12}, niacinamide, folic acid, calcium pantothenate, biotin, ascorbic acid, choline chloride, inositol, potassium phosphate, magnesium chloride, ferrous sulfate, zinc sulfate, cupric sulfate, potassium iodide, sodium selenite, sodium chloride, potassium chloride, potassium citrate, L-methionine, taurine, L-carnitine.

‡ A source of arachidonic acid (ARA).

§ A source of docosahexaenoic acid (DHA).

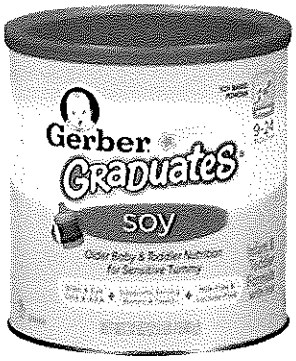
Preparation of Feedings

Product Characteristics

References

Intended for U.S. Healthcare Professionals Only

Gerber
Start Healthy Stay Healthy.



GERBER® GRADUATES® Soy

GERBER® GRADUATES® Soy formula is a milk-free and lactose-free formula for older infants and toddlers (9 to 24 months) transitioning to solid foods.*

- 100% soy protein partially hydrolyzed formula that is easy to digest
- Milk-free and lactose-free
- With the calcium a growing toddler needs
- DHA to support cognitive development[1-5]
- Kosher and halal

*Standard formulas provide adequate nutrition for the first year. GERBER® GRADUATES® formulas provide nutrition assurance.

Nutrition Information

Ingredients

GRADUATES® Soy - Powder Ingredients

CORN MALTODEXTRIN, VEGETABLE OILS (PALM OLEIN, SOY, COCONUT, AND HIGH-OLEIC SAFFLOWER OR HIGH-OLEIC SUNFLOWER), ENZYMATICALLY HYDROLYZED SOY PROTEIN ISOLATE, SUCROSE, AND LESS THAN 2% OF: CALCIUM PHOSPHATE, POTASSIUM CITRATE, POTASSIUM PHOSPHATE, SODIUM CITRATE, CALCIUM CITRATE, *M. ALPINA*,* *C. COHNII*,† MAGNESIUM CHLORIDE, CALCIUM CHLORIDE, SOY LECITHIN, FERROUS SULFATE, ZINC SULFATE, COPPER SULFATE, POTASSIUM IODIDE, MANGANESE SULFATE, SODIUM SELENATE, SODIUM ASCORBATE, CHOLINE CHLORIDE, INOSITOL, ALPHA-TOCOPHERYL ACETATE, NIACINAMIDE, CALCIUM PANTOTHENATE, VITAMIN A ACETATE, RIBOFLAVIN, THIAMINE MONONITRATE, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, BIOTIN, PHYLLOQUINONE, VITAMIN D_3, VITAMIN B_{12}, ASCORBYL PALMITATE, MIXED TOCOPHEROLS, L-METHIONINE, TAURINE, L-CARNITINE.

Note: Information is subject to change. Please read the formula label for the most up-to-date nutritional information and preparation instructions.

Appendix F

Material Safety Data Sheet
L-Methionine

MATERIAL SAFETY DATA SHEET

L-METHIONINE USP/FCC

Material no.		Version	2.8 / US
Specification	140323	Revision date	08/27/2011
Order Number		Print Date	09/28/2011
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1. IDENTIFICATION OF THE SUBSTANCE/PREPARATION AND OF THE COMPANY/UNDERTAKING

For Food, Drug or Cosmetic Use Only

Product information

Trade name	:	L-METHIONINE USP/FCC
Use of the Substance / Preparation	:	Pharmaceutical intermediate
Company	:	Evonik Degussa Corporation USA 379 Interpace Parkway Parsippany,NJ 07054 USA
Telephone	:	973-541-8000
Telefax	:	973-541-8040
US: CHEMTREC EMERGENCY NUMBER	:	800-424-9300
CANADA: CANUTEC EMERGENCY NUMBER	:	613-996-6666
Product Regulatory Services	:	973-541-8060

2. HAZARDS IDENTIFICATION

***** EMERGENCY OVERVIEW *****

***Form**-crystalline* ***Color**-white* **Odor**-*Mild, characteristic odor.*

Dust may be irritating to respiratory tract.
Fine dust, which may be formed through abrasion during transport or handling, can form explosive mixtures with air

POTENTIAL HEALTH EFFECTS

Eye contact

Possibly irritating.

Skin Contact

Not expected to be absorbed through skin.

Inhalation

May cause irritation to the respiratory tract.

Ingestion

Regarded as essentially non-toxic by ingestion.

MATERIAL SAFETY DATA SHEET
L-METHIONINE USP/FCC

Material no.		Version	**2.8 / US**
Specification	**140323**	Revision date	**08/27/2011**
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3. COMPOSITION/INFORMATION ON INGREDIENTS

Other information

This product does not contain any components considered to be health hazards under the OSHA Hazard Communication Standard 29 CFR 1910.1200 or under the WHMIS Controlled Product Regulations in Canada.

4. FIRST AID MEASURES

Inhalation

If inhaled, remove to fresh air. If breathing is difficult, give oxygen. If unconscious, evaluate the need for artificial respiration. Get immediate medical attention.

Skin contact

Wash with water and soap as a precaution.

Eye contact

In case of contact, immediately flush eyes with plenty of water. Obtain medical attention if irritation develops.

Ingestion

If swallowed, rinse mouth with water, then drink large quantities of water to rinse throat and dilute stomach contents. Never give anything by mouth to an unconcious person.
Consult a physician immediately.

5. FIRE-FIGHTING MEASURES

Suitable extinguishing media

Use water spray or fog, foam, dry chemical or CO2.

Specific hazards during fire fighting

In the case of fire, the following hazardous smoke fumes may be produced: flammable smouldering gases nitrogen oxides (NOx) Sulphur oxides In the event of fire and/or explosion do not breathe fumes.

Special protective equipment for fire-fighters

As in any fire, wear self-contained positive-pressure breathing apparatus, (MSHA/NIOSH approved or equivalent) and full protective gear.

Further information

Avoid dust formation.

6. ACCIDENTAL RELEASE MEASURES

Environmental precautions

Obey relevant local, state, provincial and federal laws and regulations. Do not contaminate any lakes, streams, ponds, groundwater or soil.

Methods for cleaning up

Collect material and place in a disposal container.

Use cleaning techniques that do not generate dust clouds if ignition sources are present.

Dusts can form explosive mixtures with air.

Use only vacuum cleaners approved for combustible dust collection.

Additional advice

If dust is present, control smoking, open flames, sparks, static electricity and friction heat.

7. HANDLING AND STORAGE

Handling

Safe handling advice

Minimize dust generation and accumulation.
May form flammable dust-air mixtures.
Avoid breathing dust.

Advice on protection against fire and explosion

Prevent the generation of dust clouds, since dusts can form explosive mixtures with air. If dust forms, remove all sources of ignition and static discharge.

Do not allow dust to collect in open or hidden areas.
In product transfer systems involving the use of air as a fluidizing medium, the user must be sure to dissipate static charge by careful bonding and grounding of all equipment and personnel involved in fluid transfer, with continuity checks to prove effectiveness.

Additional guidance on fire and explosion protection may be found in the consensus standard NFPA 654 for chemical dusts.

Storage

Requirements for storage areas and containers

Keep away from heat. Store in a cool, dry place. Keep container closed when not in use.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Component occupational exposure guidelines

- **exposure limit for dust**

CAS-No.		
Control parameters	15 mg/m3	Time Weighted Average (TWA) Permissible Exposure Limit (PEL):(OSHA Z1)
	Total dust.	
	5 mg/m3	Time Weighted Average (TWA) Permissible Exposure Limit (PEL):(OSHA Z1)
	Respirable fraction.	

10 mg/m3 Inhalable fraction.	Time Weighted Average (TWA):(ACGIH)
3 mg/m3 Respirable fraction.	Time Weighted Average (TWA):(ACGIH)

Engineering measures

Avoid dust formation and control ignition sources. Employ grounding, venting and explosion relief provisions in accordance with accepted engineering practices in any process capable of generating dust and/or static electricity.

To identify additional system design issues with respect to dust hazards, it is recommended to conduct a dust hazard analysis using information and sources provided in the OSHA Fact Sheet on combustible dusts (DSG 3/2008) and addressing enforcement issues identified in the Combustible Dust National Emphasis Program (Reissued) (CPL 03-00-008, 3/11/08)

Personal protective equipment

Respiratory protection

A respiratory protection program that meets OSHA 1910.134 and ANSI Z88.2 or applicable federal/provincial requirements must be followed whenever workplace conditions warrant respirator use. NIOSH's "Respirator Decision Logic" may be useful in determining the suitability of various types of respirators.

Hand protection

Use impermeable gloves.

Eye protection

Wear safety glasses with side shields.

Skin and body protection

A safety shower and eye wash fountain should be readily available.
To identify additional Personal Protective Equipment (PPE) requirements, it is recommended that a hazard assessment in accordance with the OSHA PPE Standard (29CFR1910.132) be conducted before using this product.

9. PHYSICAL AND CHEMICAL PROPERTIES

Appearance

Form	crystalline
Color	white
Odor	Mild, characteristic odor.

Safety data

pH	5.6 - 6.1
Melting point/range	276 - 279 °C
Explosiveness	Dust, which can occur through abrasion, can combine with air to form a mixture which can be explosive.

MATERIAL SAFETY DATA SHEET
L-METHIONINE USP/FCC

Material no.		Version	**2.8 / US**
Specification	**140323**	Revision date	**08/27/2011**
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Bulk density 420 kg/m3

10. STABILITY AND REACTIVITY

Conditions to avoid: Operations that create dust.

Hazardous decomposition products: Sulphur oxides, nitrogen oxides (NOx), Carbon oxides

Thermal decomposition: Stable under normal conditions.

11. TOXICOLOGICAL INFORMATION

Product Acute oral toxicity: LD50 Rat: > 10000 mg/kg (literature)

12. ECOLOGICAL INFORMATION

General Ecological Information: There are no ecological data available.

13. DISPOSAL CONSIDERATIONS

WASTE DISPOSAL

Advice on disposal: Waste must be disposed of in accordance with federal, state, provincial and local regulations.

14. TRANSPORT INFORMATION

Transport/further information
Not dangerous according to transport regulations.

15. REGULATORY INFORMATION

Information on ingredients / Non-hazardous components

This product contains the following non-hazardous components

L-Methionine
CAS-No. 63-68-3 Percent (Wt./ Wt.) 100 %

US Federal Regulations

MATERIAL SAFETY DATA SHEET
L-METHIONINE USP/FCC

EVONIK INDUSTRIES

Material no.		Version	**2.8 / US**
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OSHA

If listed below, chemical specific standards apply to the product or components:

- None listed

Clean Air Act Section (112)

If listed below, components present at or above the de minimus level are hazardous air pollutants:

- None listed

CERCLA Reportable Quantities

If listed below, a reportable quantity (RQ) applies to the product based on the percent of the named component:

- None listed

SARA Title III Section 311/312 Hazard Categories

The product meets the criteria only for the listed hazard classes:

- No SARA Hazards

SARA Title III Section 313 Reportable Substances

If listed below, components are subject to the reporting requirements of Section 313 of Title III of the Superfund Amendments and Reauthorization Act of 1986 and 40 CFR Part 372:

- None listed

Toxic Substances Control Act (TSCA)

If listed below, non-proprietary substances are subject to export notification under Section 12 (b) of TSCA:

- None listed

State Regulations

California Proposition 65

A warning under the California Drinking Water Act is required only if listed below:

- None listed

MATERIAL SAFETY DATA SHEET
L-METHIONINE USP/FCC

Material no.		Version	**2.8 / US**
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International Chemical Inventory Status

Unless otherwise noted, this product is in compliance with the inventory listing of the countries shown below. For information on listing for countries not shown, contact the Product Regulatory Services Department.

• Europe (EINECS/ELINCS)	Listed/registered
• USA (TSCA)	Regulated food, drug, cosmetic
• Canada (DSL)	Listed/registered
• Australia (AICS)	Listed/registered
• Japan (MITI)	Listed/registered
• Korea (TCCL)	Listed/registered
• Philippines (PICCS)	Listed/registered
• China	Listed/registered

16. OTHER INFORMATION

HMIS Ratings

Health :	0
Flammability :	N
Physical Hazard :	0

Further information

Changes since the last version are highlighted in the margin. This version replaces all previous versions.

The information provided in this Safety Data Sheet is correct to the best of our knowledge, information and belief at the date of its publication. The information given is designed only as a guidance for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered a warranty or quality specification. The information relates only to the specific material designated and may not be valid for such material used in combination with any other materials or in any process, unless specified in the text.

Appendix G

Institute of Medicine
Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids

A lim i talion or th ese cl in ical studies is that they were clone i n h um ans with a disease. Also, th e l ongest study was on ly 6 mon ths. Finally, only a l im i ted n um ber or end poi n ts were i nvestigated. McCune and coworkers (1984) reponed n o effects on plasm a sodi u m, potassi u m, and chlorid e i n 41 pati en ts treated for 24 weeks wi th 1,248 mg/ d of L-lysi n e m onohydroch loride.

Dose–Response Assessment

As mention ed above, very few adverse effects of L-lysi ne have been observed in h u mans or animals arter h igh , mostly acute, closes. Thus, the data on the adverse effects of L-lysine from supplements were considered not suffi cien t for a close-response assessmen t and derivalion of a UL for apparently healthy humans.

Methionine

L-Methioni ne i s an i ndispensable am ino aci d wi th glycogen ic properties. In ani mal studi es, i t has been described as one or the more toxic am i no acids (Heal th and Welfare Can ada. 1990) . Hu mans, as well as other mam mals. can not fix i norgan ic sulfu r in to organic molecu les and must rely on ingested su l fur am i n o acids, such as meth ionine, for the syn thesis of protein and biological ly aclive sul fur. Based on distribution data from the 1988-1994 N HAN ES III , the mean daily i n take for all l ife stage and gender grou ps of m eth ionine from rood and supplemen ts i s 1 .8 g/ cl (Appendix Table D- 12). Men 51 through 70 years of age had th e highest in takes at the 99th percen Lile or 4.lg/cl .

Hazard Identification

Adverse Effects iu Animals. Dietary excesses of L-m eth ion i n e (2.7 percen t of the cl iet) for 6, 13, or 20 clays have been associated wi th erythrocyte engorgemen t and accum ulalion of hemosidcri ne in rats (Beneven ga et al., 1976) , and there was a depression of growth and splenic damage. A single d ietary dose (2.7 percent of the diet) of L-methionine decreased body growth and also reduced food intake i n rats (Steele et al., 1979) .

Dietary i n takes of 2 to 4 percent of L-m eth ionine caused sl igh t changes i n liver cells in rats (Stckol and Szaran, 1962) and sligh t decreases in liver iron conten t (Klavi ns et al., 1963). Darkened spleens caused by increases i n i ron deposi tion have been observed i n wean li ng rats fed I .8 percen t m eth ionine diets for 28 days (Celan der and George, 1963).

Viau and Lcathcm (1973) fed pregnant rats 4 percen t of their diet as methion ine and reported subnormal fetal and pl acental weights. However, suppl emen tal meth ion i ne preven ted n eural tu be defects in rat em bryos treated wi th teratogen i c amiviscera J yolk sac serum (Fawcett et a l., 2000) . I n th e mouse , th e adm i nistration of meth i onine red uced experi men tally ind uced spina bifida (Eh lers ct al., 1994). Other studies in roden t and pri ma te models support the beneficial effect of methionine supplemen ta ti on in im provi ng pregn ancy outcomes (Cham bers et a l., 1995; Chatot ct al., 1984; Coel h o a nd Klein , 1990; Ferra ri et al., 1994; Mocphul i ct al., 1997).

Adverse Effects in H1111al Is. Si n gle oral doses of about 0.6 g (adults) and 0.08 g (i n fants) l ed to i ncreased plasma l evels of L-meth ioni ne and L-alan in e, and dcercascel plasma concen u-at.ion s or leucine, isoleucine, val inc, tyrosine, Lryptophan, and phenylalan i n e (Stegi nk et al., 1980, 1982b). Ne i th er report i n cl ud ed m en ti on or any adverse effects. Meth ion i ne su pplem en ts (5 g/d) for periods or weeks were reportedly in nocuous in h um ans (H eal th a nd Welfare Canada, 1990) . A single oral dose of 7 g has been associated wi th i n creased plasma concen trations of meth ionine and the presen ce of m ixed sulfides (Brattstrom et al., J 984). Single oral doses or 7 g produced leth argy i n six individuals and oral admin istration or / 0.5 g of L-mcth ioni n c to one produced n ausea and vom i ting (Perry et al., 1965). After an oral ad m i n isu·ati on or 8 g/d or meth ioni ne (isomer not specified) for 4 days, scrum fola Le concen trations were decreased in five otherwise healthy ad u lts (Con nor ct al., 1978).

High doses or m eth ion i ne (- I 00 mg/ kg of body weigh t) led Lo elevated plasma m eth ion i n e and h omocystcine concen trations (Brattstrom et al., 1984, I 990; Clarke ct al., 1991; Wilckcn et al., 1983) . Thus, it was concl uded that el evated plasma h omocysteine concenu·ations may be a risk factor for coronary disease (Clarke et al., J 991) .

Infan ts more rapidly metabolized meth ioni ne than adults (Stegink et al., 1982b). In women whose average daily intake of methioni ne was above the lowest quartile of i n take (greater than J .34 g/ d), a 30 Lo 40 percen t reduction in neural tube defect-affected pregnancies was observed (Shaw et al., 1997). These reduction s were observed for both an encephaly an d spina bifida.

Dose–Response AssPssmenl

There arc no adequate data to characterize a dose-response relationship for lrmcth ion in c. Thus the data on the adverse effects of L-methion i ne from supplements were consid ered n ot sufficient for a dose-response assessmcnL and derirntion or a U L for appa ren tly heal thy humans.

Appendix H

ESPGAN Committee on Nutrition Report Comment of the Composition of Soy Protein Based Infant and Follow-Up Formulas

Acta Padiatr Scand 79: 1001-1005, 1990

COMMITTEE REPORT

Comment on the Composition of Soy Protein Based Infant and Follow-up Formulas

ESPGAN COMMITIEE ON NUTRITION: P. J. AGGETI (Secretary), F. HASCHKE, W. HEINE, 0. HERNELL, K. LAUNIALA, J. REY (Chairman), A. RUBINO, G. SCHOCH, J. SENTERRE and R. TORMO

The ESPGAN Committee on Nutrition has published recommendations for the composition of adapted formulas (1) and follow-up formulas based on cow's milk (2, 3). This report considers the composition of infant and follow-up formulas based on soy isolate proteins. The clinical indications for soy isolate protein products are debatable. Indications for which they are often used are: (a) adverse reactions to cow's milk protein, (b) a requirement for lactose and/or galactose free diets, and (c) an alternative for those who wish to avoid giving their infants formulas containing animal products (4). Although the second and third indications justify the choice of a soy-based formula, the Committee considers that available data do not support the view that such formulas should be the preferred choice when suspected, or proven adverse effects to cow's milk protein is the indication (5, 6). Certainly the availability of soy-based products should not compromise the important concept, that an infant's own mother's milk is the most appropriate feed.

ENERGY

Soy based infant formulas

250-315 kJ·dl-^{1} (60-75 kcal·dl-^{1})

Soy basedfollow-up formul as

250-335 kJ ·dl-^{1} (60-80 kcal· dl-^{1})

The metabolisable energy content of infant feeding formulas based on soy-protein isolates is similar to that of formulas based on cow's milk. The Committee can therefore consider that the energy density of these formulas can correspond to recommendations which have already been made for infant formulas and follow-up formulas based on cow's milk protein (1, 3).

PROTEIN

Soy based infant formulas

0.564l.7 g· 100 kJ- ^{1}
2.25–3.0 g· 100 kcal-^{1}
1.35–2.25 g•dl-^{1}

NB.: Minimum methionine content of 7.3 mg (50 µmo!), 100 kJ-¹, i.e. 30 mg (200 µmol)·lOO kca1-¹. Minimum L-carnitine content of 0.3 mg (1.8 µmol)·1 OO kJ-¹, i.e. 1.2 mg (7.5 µmol)· 100 kca1- ¹

Soy based follow-up formulas

0.7-1.1 g· 100 kJ-¹
3.0-4.5 g ·100 kcal -¹
1.8-3.6 g ·dJ- ¹

NB.: Minimum methionine content of 7.3 mg (50 µmol)· 100 kJ-¹, i.e. 30 mg (200 µmol)· 100 kcal- ¹· L-carnitine content of 0.3 mg (1.8 µmol)· 100 kJ-¹, i.e. 1.2 mg (7.5 µmol)·100 kca1- ¹

Unmodified soy based milks are considered unsuitable for infants because of side effects caused by raffinose and stachyose (7). Isolated soy protein if appropriately processed is a good vegetable protein source for children (7). Ithas a high nutritional value and its amino acid composition rating is 96% that of casein, and even after allowance bas been made for digestibility, the amino acid score is 89% overall and still remains above 80% when the least available amino acid, methionine, is considered, but nevertheless this is limiting (8). Thus even when protein intake is not marginal methionine supplements are needed to ensure growth, and to maintain nitrogen balance and circulating plasma albumin concentrations (9). The Committee considers therefore, that soy protein isolate based infant and follow-up formulas should contain at least 30 mg (200 µmol) of methionine· JOO kcal-¹ (50 µmol (7.3 mg)· 100 kJ-¹) approximating to the amount in human breast milk.

In contrast to human breast milk and formulas based on cow's milk protein , soy based products contain no intrinsic L-carnitine (l0), the function of which is to transfer fatty acids into the mitochondria . The newborn infant has a finite store of carnitine which, in the absence of an exogenous supply, could be depleted by two and a half months (l l-14). Therefore, although there is, with one possible exception (15), no conclusive evidence that infants fed soy based products are at serious risk of developing carnitine deficiency (11), the Committee consider it prudent to support the view that soy based products should be supplemented to a level approximating that in human breast milk.

FAT

Soy based infant formulas and soy based follow-up formulas

0.9-1.4 g· 100 lcJ-¹

4.(µj.0 g· 100 kcal- ¹

Since soy protein isolates are lipid-free, fat needs to be added. This is done by manufacturers using varying proportions of vegetable oils such as sunflower, safflower, coconut, palm, com (maize) and occasionally oleo oils, thereby offering considerable opportunity to manipulate the lipid composition of the products. The Committee, at present, is not aware of any metabolic indications for using vegetable fats to the complete exclusion of animal fats though they appreciate that in some circumstances this may be preferred on cultural grounds. We see no reason at

present to have different recommendations on the lipid content from those recommended for infant formulas and follow-up formulas based on cow's milk protein (3). The lipid composition of infant formulas will be reviewed by the Committee in the future.

CARBOHYDRATE

Soy based infant formulas and soy based follow-up formulas

2.0-3.0 g ·100 kJ^{-1}
8.0-12.0 g·100 kcal^{-1}

The absence of lactose from soy protein isolates has enabled the use of alternative carbohydrate sources and, thereby, the therapeutic use of soy based products in the management of children who need to avoid either lactose or galactose or both. Additionally since the facilitative effects of lactose on mineral absorption could be achieved also by glucose polymers the Committee discourages the specific supplementation of soy based products with lactose. Ifhowever lactose is present in such formulas the Committee recommends that the products should be labelled as "lactose containing".

Starch is sometimes added to .soy based infant formulas, in which case it should be gluten free and starch should not exceed 3 g·100 kcal^{-1} The addition of sucrose should be discouraged, but th Committee agrees that the amount of sucrose and, in the case of follow-up formula\, fructose and honey added separately or as a whole should not exceed 20 % of thetotal carbohydrate content (16).

MINERALS

Calcium and phosphorus
Soy based infant formulas

Calcium: minimum	14 mg· 100 1cJ^{-1}
	60 mg· 100 kcal^{-1}
	40 mg·dl^{-1}
Phosphorus:	7.2-12 mg· 100 kJ^{-1}
	30-50 mg· 100 kcal^{-1}
	20-35 mg·dl^{-1}

Ca: P ratio: not less than 1.2 and not more than 2.0.

Soy based follow-up formulas

Calcium: minimum	22 mg· 100 lcJ^{-1}
	90 mg· 100 kcal^{-1}
	60 mg·dI^{-1}
Phosphorus:	14 mg· 100 1cJ^{-1}
minimum	60 mg·100 kcal^{-1}
	40 mg·dl^{-1}

Ca: P ratio: not less than 1.0 and not more than 2.0.

Soy based products, which have not been designed specifically for infants, are poor in calcium but rich in phosphorus, and infants fed these products have developed overt rickets (17). Poorer mineralisation of bone has also been observed

in infants receiving a soy protein isolate based infant formula, when compared with those fed infant formulas based on cow's milk protein (18, 19). However, these differences which were present at 3 months of age had disappeared at 6 months of age, and infants followed up until 1 year of age had bone mineralisation similar to those of breast fed and vitamin D supplemented infants (18, 19). Therefore the Committee recommends that the calcium and phosphorus content of soy based infant formulas and follow-up formulas should be similar to those for cow's milk based formulas (1, 3).

Iron and zinc

Iron 0.24-0.48 mg (4.3–8.6 μmol)· 100 kJ-^{1} i.e. 1.0-2.0 mg (18.0-36 μmol)· 100 kcal^{-1}.

Zinc Minimum 0.18 mg (2.8 μmol)·lOO kJ-^{1}, i.e. 0.75 mg (11.5 μmol)·l00 kcaJ-^{1}, with a maximum iron :zinc molar ratio of 2.5: 1.

Native soy protein has a high (1-1.5%) content of phytate (inositol hexaphosphate) which is a potent chelator and inhibitor of the absorption of trace elements such as iron (20-23) and zinc (24-27). Evidently the ideal solution to the limited availability of iron and zinc from soy based formulas would be to remove all their phytate content. In the absence of achieving this the Committee feels that there is a need to enrich these products with both iron and zinc.

Interactions which limit intestinal uptake and transfer of some trace metals also occur between inorganic elements, thus iron may interfere with the utilisation of zinc and vice versa (28). Hence, it is important to consider the relative proportions of these metals in infant formulas and follow-up formulas. Although, in the future, it may be necessary to comment on the amount of copper, for the moment we make a recommendation only for iron and zinc in that we feel that the iron :zinc molar ratio should not exceed 2.5. The Committee proposes that, in contrast to the provision for cow's milk based formulas, soya protein isolate based products should be enriched with iron at 1.0-2.0 mg (18.0-36 μmo))· 100 kcaI-^{1}.

VITAMINS

The Committee considered that there was no reason to deviate from the Codex recommendations on vitamins which have been provided for cow's milk based infant formulas and follow-up formulas.

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Lisa M. Brines, Ph.D.
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Sent by email [lisa.brines@ams.usda.gov]

Dear Dr. Brines:

Re: Petition for L-Methionine – 6. Ancillary Substances.

Thank you for your letter dated June 15, 2016 regarding our need to provide documentation on ancillary substances.

We have contacted our vendor of L-Methionine (DSM Nutritional Products) for the necessary information on whether any ancillary substances were used in the manufacturing of L-Methionine. We also requested verification that the manufacturer of L-Methionine being used by DSM Nutritional Products is Evonik-Rexim Pharmaceutical Company as noted in our petition dated April 4, 2016.

I have attached both responses from DSM Nutritional Products verifying that Evonik-Rexim Pharmaceutical Company is the manufacturer and that there are no ancillary substances used in the manufacturing of L-Methionine.

Thank you for your assistance in completing the necessary information for our petition on L-Methionine. Please let me know when our petition will be reviewed by the National Organic Standards Board.

Sincerely,

Jay Highman, President
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Raw Material (L-Methionine) Statement

30 June 2016

PRODUCT CODE: FT111172
PRODUCT NAME: WSV BOO USA Soy

According to information provided to DSM Nutritional Products, LLC by its raw material suppliers, the L-Methionine contained in the above-named product does not contain any ancillary substances.

If you have any questions or need further information, please contact your Customer Service Representative.

Best regards,

Alysia Sawyer
Documentation Specialist

DSM
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Raw Material – L-Methionine Statement

14 July 2016

PRODUCT CODE: FT111172
PRODUCT NAME: WSV BOO USA Soy

The manufacturer currently certified as the supplier of L-methionine in the above-named product code is as follows:

Evonik-Rexim Pharmaceutical Company, a Division of Evonik Industries AG in Essen, Germany.

Evonik Rexim (Nanning) Pharmaceutical Co., Ltd
No. 10, Wenjiang Road
Wuming County
530100 Nanning, China

c/o Evonik Degussa Corp. USA
299 Jefferson Road
Parsippany, NJ 07054
Tel.: 973-929-8000
Fax.: 973-929-8013

If you have any questions or need further information, please contact your Customer Service Representative.

Best regards,

Alysia Sawyer
Documentation Specialist