Petition for addition to the National List of the substance INOSITOL, for use in infant formula products labeled as "organic."

INTRODUCTION

In October 1995, the National Organic Standards Board (NOSB) received a recommendation from its Processing, Handling and Labeling Committee (the Committee) regarding the inclusion of synthetic vitamins, minerals, and accessory nutrients in organic foods.

The Committee had debated the issue of the inclusion of synthetic vitamins, minerals, and/or accessory nutrients in organic foods. Although it is generally considered that foods themselves are the best source of nutrients, in some cases, State regulations mandate the inclusion of vitamins, minerals and/or accessory nutrients to fortify foods.

The Committee also believed that recommendation by independent professional associations may also be taken into consideration. An example of this is infant cereals in which fortification of iron is highly recommended by the American Dietetic Association and various associations dealing with pediatric care and nutrition as a baby's stored iron supply from before birth runs out after the birth weight doubles.

The NOSB approved a Final Board Recommendation (FBR) in October 1995. The Final Board Recommendation reads as follows:

> **"**Upon implementation of the National Organic Program, the use of synthetic vitamins, minerals, and/or accessory nutrients in products labeled as organic must be limited to that which is required by regulation or recommended for enrichment and fortification by independent professional associations."

The FBR includes a definition of the term "accessory nutrients," to mean nutrients not specifically classified as a vitamin or mineral but found to promote optimal health. Examples relevant to the foods known as infant formulas and cited in the FBR are omega-3 fatty acids, inositol, choline, carnitine, and taurine.

Infant formulas serve as the sole item of diet of infants who are not human milk-fed for the first four to six months of life. Several accessory nutrients are included in infant formula for one or more of the following reasons:

1. their inclusion has been shown to enable infants fed these formulas to grow and develop similar to infants fed human milk;
2. their inclusion provides the infant with the same quantity of an accessory nutrient provided by human milk; and
3. the accessory nutrient is essential for one or more other species of mammal, which is indirect evidence of their biological essentiality for man.

In creating the current regulation for organic foods, Code of Federal Regulations, Title 7, Part 205, the USDA implemented the FBR with respect to permitting the addition of nutrient vitamins and minerals at §205.605(b), albeit with an annotation ("in accordance with 21CFR 104.20")

different than that approved by the NOSB. However, the current regulation is silent with respect to accessory nutrients.

On November 3, 2006, the USDA National Organic Program (NOP) notified Accredited Certifiers that they could allow additional nutrients to be utilized in products certified as "organic" in accordance with 21 CFR 104.20(f).

In 2011 the Food and Drug Administration (FDA), at the request of NOP, provided its interpretation that 21 CFR 104.20(d)(3) includes only those nutrient vitamins and minerals listed in 21 CFR 104.20(d)(3) and those identified as essential nutrients in 21 CFR 101.9.

On April 26, 2011, the Deputy Administrator of the National Organic Program announced its intention to publish draft guidance that will clarify the allowance under the NOP regulation §205.605(b), according to the Food and Drug Administration's interpretation of 21 CFR 104.20.

Infant formulas are regulated by the Food and Drug Administration and are established in the Code of Federal Regulations, Title 21, Parts 106 and 107. 21 CFR 107.10 and 107.100 cite the essential and approved nutrients required for infant formula. Not all of the required nutrients for infant formula are listed in 21 CFR 104.20(d)(3) or identified as essential nutrients in 21 CFR 101.9. Consequently, these exceptional nutrients must be petitioned for addition to the National List to enable all infant formulas marketed in the United States both to comply with the FDA regulation and to qualify for being labeled as "organic" according to the NOP regulation.

This petition specifically requests addition of the nutrient inositol to the National List for use in infant formulas labeled as "organic." This action is consistent with the 1995 FBR, since the applicable FDA infant formula regulations, published Oct. 30, 1985 [50 FR 45108], predate the FBR.

ITEM A

This petition seeks inclusion of **INOSITOL** on the National List at §205.605(b) as a non-agricultural (non-organic) substances allowed as an ingredient in or on processed products labeled as "organic" or "made with organic (specified ingredients)."

ITEM B

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

Inositol (*myo*-inositol) ($C_6H_{12}O_6$) is a six-carbon cyclic sugar-related alcohol that is abundant in many mammalian tissues. Its other names include *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol, hexahydroxycyclohexane, cyclohexitol, meat sugar, rat antispectacled eye factor, and mouse antialopecia factor. The last two names reflect the symptoms of inositol deficiency seen in the rat and the mouse, two mammalian species in which inositol deficiency has been observed.

Inositol exists in plants as its hexaphosphate derivative, which is known as phytic acid. The digestive systems of most mammals cannot hydrolyze phytic acid, so this inositol is not available

to the infant. Inositol exists in animal tissues as a component of phospholipids. Cows' milk contains only a third to a quarter as much inositol as the average human milk.

Inositol is synthesized from phytic acid, which is produced by plants, especially cereals and beans. The manufacturing process for inositol starts with an agricultural byproduct, such as corn steep water or defatted rice bran. The phytic acid is hydrolyzed with steam and pressure, yielding inositol and mineral phosphates. This simple and sustainable process has little risk of environmental contamination or toxicity.

2.a. The petitioner's name, address and telephone number and other contact information.

International Formula Council, 1100 Johnson Ferry Road NE, Suite 300, Atlanta, GA 30342
Contact: Mardi Mountford, Executive Vice President
Phone: (678) 303-3027 Email: mmountford@kellencompany.com

2.b. Manufacturer names, addresses and telephone numbers and other contact information.

Tsuno Rice Fine Chemicals Co., Ltd., 2283 Chonomachi, Katsuragi-Cho, Ito-Gun, Wakayama, 649-7194, Japan
Phone: 81-0-736-22-8000 FAX: 81-0-736-22-6069 Web: http://tsuno.co.jp

Zhucheng Haotian Pharm Co., Ltd., 64 Jiangjun Road, Xinxing, Zhucheng, Shandong, China
Phone: 6520115 6523366 FAX: 86 536 6523666 Web: http://www.zcht.cc

3. The intended or current use of the substance such as use as a nonagricultural ingredient.

Inositol is currently listed in the FDA's Infant Formula regulation, as a nutrient required to be declared on the label, at 21 CFR 107.10, and to be added to non-milk-based infant formula, at 21 CFR 107.100(a). This petition seeks to add the nutrient inositol to the National List to permit its addition as a nonagricultural ingredient in infant formula.

The inositol content of human milk is between 22mg/100 kcal and 48 mg/100 kcal, with the standard value being considered to be 40 mg/100 kcal. Unless fortified with inositol, a cow milk-based infant formula could provide the infant with only 20% as much inositol as he or she would get from his or her mother's milk. Appendix F in the 1998 LSRO report show a minimum level of only 4.7 mg/100 kcal in commercial infant formula. The current FDA regulation requires that non-milk-based formulas contain not less than 4 mg/100kcal, with no maximum. The 1998 report by the Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences developed for the Center for Food Safety and Applied Nutrition of the FDA in coordination with the Committee on Nutrition of the American Academy of Pediatrics and the Food and Nutrition Board of the Institute of Medicine recommended that all infant formula should contain between a minimum of 4 mg/100 kcal and a maximum of 40 mg/100 kcal.

International standards for infant formula also allow fortification of all types of infant formulas, up to the human milk level, 40 mg/100 kcal, with a minimum of 4 mg/100 kcal.

4. A list of the handling activities for which the substance will be used and its mode of action.

Inositol is currently added as a nutrient ingredient to infant formulas labeled as "organic."

Inositol is used in the body to make phosphorylated lipid derivatives and glycosyl-phosphatidylinositol anchors of membrane lipids. These compounds act as cellular mediators in signal transduction, growth, and metabolism regulation.

Inositol is required for synthesis of phosphatidyl glycerol, a primary component of lung surfactant. The synthesis of lung surfactant is a major regulatory feature of lung development, and its deficiency results in significant impairment of respiratory function (i.e., respiratory distress syndrome), a condition commonly associated with prematurity in infants. A potential benefit of inositol supplementation has been reported in both animals and premature infants.[1,2,3]

Providing inositol to preterm infants increases plasma inositol concentrations, reduces neonatal mortality, increases survival without chronic lung disease, and decreases the incidence and severity of retinopathy of prematurity, all findings consistent with inositol deficiency and subsequent adverse effects in the preterm infant.[4]

In a study evaluating the effect of diet on preterm infant serum inositol levels, human milk-fed infants had substantially higher levels of inositol during the first three weeks of life than those fed infant formula (without added inositol).[5]

5. The source of the substance and a detailed description of its manufacturing process.

Inositol can be produced from corn steep water, in which it is present as phytic acid. Phytic acid in an acid solution such as corn steep liquor can be precipitated as "phytin," the phytic acid complex with calcium and magnesium, by addition of alkali (calcium hydroxide, sodium carbonate, etc.). Heating phytin with water under pressure removes the phosphate groups, liberating free inositol. U.S. Patent Numbers 2,112,553 and 2,414,365 describe this simple process in detail and are available in Appendix A.

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[1] Life Sciences Research Office (LSRO) Report: Assessment of Nutrient Requirements for Infant Formula, 1998. J. Nutr. 1998;128(11Supp): 2129S.
[2] Hallman M, Bry K, Hoppu K, Lappi M, Pohjavuori M. Inositol supplementation in premature infants with respiratory distress syndrome. N Engl J Med. 1992 May 7;326(19):1233-9.
[3] Hallman M, Arjomaa P, Hoppu K. Inositol supplementation in respiratory distress syndrome: relationship between serum concentration, renal excretion, and lung effluent phospholipids. J Pediatr. 1987 Apr;110(4):604-10.
[4] Hallman M, Järvenpää AL, Pohjavuori M. Respiratory distress syndrome and inositol supplementation in preterm infants. Arch Dis Child. 1986 Nov;61(11):1076-83.
[5] Pereira GR, Baker L, Egler J, Corcoran L, Chiavacci R. Serum myoinositol concentrations in premature infants fed human milk, formula for infants, and parenteral nutrition. Am J Clin Nutr. 1990 Apr;51(4):589-93.

One of the suppliers listed in 2b, Tsuno Rice Fine Chemicals Co., Ltd., produces inositol from defatted rice bran. Details of the process also are available in Appendix A. Defatted rice bran is extracted with acidified water at a pH of 3 to 4 (the approximate pH of the human stomach). The filtrate is neutralized with alkali to precipitate phytin. The phytin is heated in water at high temperature (190°-230°C) and pressure to hydrolyze the phosphate groups and liberate inositol. The aqueous filtrate contains the inositol and the precipitate is calcium phosphate. The filtrate is decolorized and demineralized with ion exchange resins, and the inositol is crystallized and dried.

6. A summary of any available previous reviews of inositol.

a. Life Sciences Research Office of the American Societies for Nutritional Sciences (LSRO). Assessment of Nutrient Requirements for Infant formulas. J Nutr 1998;128(11Supp):2059S–2298S. (under contract for the FDA). Page 2067S:

> ***Minimum:*** **The Expert Panel recommended a minimum content of *myo*-inositol in infant formulas of 4 mg/100 kcal.** Although the essentiality of dietary *myo*-inositol for infants remains an open question, it is an essential nutrient for at least two other species of mammals. Until more data on the requirement for *myo*-inositol are available, it seems prudent to reaffirm the CFR value of 4 mg/100 kcal.
>
> ***Maximum:*** **The Expert Panel recommended a maximum content of myo-inositol in infant formulas of 40 mg/100 kcal.** Although current usage data are not available, this value is near the upper limit reported for human milk.

b. Scientific Committee on Food. Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae. Brussels, European Commission 2003. SCF/CS/NUT/IF/65 Final 2003. Page 73:

> **2.4 Inositol**
> The most common form of inositol in mammalian tissues and cells is myoinositol, a six carbon cyclic sugar related alcohol. It is found in the free form as phosphorylated lipid derivatives, phosphoinositides, and in membranes as glycosyl-phosphatidyl inositol where it plays an important structural and functional role in signal transduction and metabolic regulation (Aukema and Holub, 1994; LSRO, 1998). Physiologically, inositol is an essential growth factor, which is readily synthesised in the body, but may need to be provided in the diet under certain conditions. The form in which inositol occurs most commonly in plants is as phytate, and when phytate is taken in the diet it may limit the bioavailability of minerals with which it forms complexes, such as iron, copper and zinc.
>
> Inositol is present in high concentration in human milk, and decreases over the course of lactation. The reported concentrations range from 22 to 48 mg/100 kcal (Bromberger and Hallman, 1986; Ogasa *et al.*, 1975; Pereira *et al.*, 1990). Inositol levels in blood are high in neonates, leading to the suggestion that it plays an important role in early development. Over a three week period the serum concentration of myoinositol increased in infants receiving human milk, but not in those receiving formulae (Pereira *et al.*, 1990). A possible role has been suggested for the formation of surfactant and lung development (Anceschi *et al.*, 1988; Hallman *et al.*, 1992), the prevention of the development of

retinopathy of prematurity (Friedman *et al.*, 2000), and necrotising enterocolitis (Carlson *et al.*, 1998). There are no studies on the effect of inositol on growth and development, nor on its safety.

In the USA, inositol needs to be added to non-milk-based formula at 4 mg/100 kcal (FDA, 1985).

The LSRO Expert Panel (1998) recommended that the minimum content of myoinositol should be 4 mg/100 kcal, and the upper level should be 40 mg/100 kcal, which is around the upper level reported for human milk.

The Committee proposes a minimum content of myoinositol of 4 mg/100 kcal and a maximum content of myoinositol of 40 mg/100 kcal for infant formulae, while no limits are suggested for follow-on formulae.

c. Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group. ESPGHAN Committee on Nutrition. Journal of Pediatric Gastroenterology and Nutrition, 41:584–599 November 2005. Page 596:

Myo-inositol
The recommendations of previous expert reviews for a myo-inositol content of 4–40 mg/100 kcal are supported.

7. Regulatory status.

Inositol is recognized as a Generally Recognized as Safe (GRAS) substance and is listed at 21 CFR 184.1370 (see Appendix B). Appendix B also contains the Food Chemicals Codex monograph for inositol.

Infant formulas are regulated by the Food and Drug Administration. The regulations for infant formula are established in the Code of Federal Regulations, Title 21, Parts 106 and 107. §107.10 and §107.100 list the essential and approved nutrients required for infant formula. Inositol is recognized as an essential nutrient in infant formula at §107.10 and §107.100(a). See Appendix B for copies of these two sections of the FDA regulation.

The FAO/WHO Codex Alimentarius Commission adopted an international standard for infant formula in 1976 and adopted amendments in 1983, 1985, and 1987. They further revised the standard in 2007. CODEX STAN 72-1981 (available in Appendix B) requires a minimum level of 4 mg/100 kcal of inositol in all infant formulas and sets a guidance upper level (GUL) of 40 mg/100 kcal.

8.a. The Chemical Abstract Service (CAS) number of inositol is 87-89-8.

8.b. Labels of products that contain inositol are included as Appendix C.

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

Inositol occurs as fine, white crystals or as a white crystalline powder. Its solutions are neutral to litmus. It is stable in air. One gram is soluble in 6 mL of water. It is slightly soluble in alcohol, and is insoluble in ether and in chloroform. Inositol has a mild sweet taste, which is consistent with its sugar-alcohol structure.

Inositol is a growth factor for animals and microorganisms. An internet search found no evidence of drug interactions in humans.

Inositol is used in the body for synthesizing essential phospholipids, such as lung surfactant. The bodies of healthy, mature animals synthesize sufficient inositol from glucose if dietary sources are inadequate.

Inositol is one of the most abundant metabolites in the human brain and is located mainly in glial cells where it functions as an osmolyte. The concentration of inositol is altered in many brain disorders including Alzheimer's disease and brain tumors. Adolescent chronic marijuana smokers show a significant 10% reduction in inositol concentrations in the anterior cingulum structure in the brain, indicating altered glial cell metabolism.

Inositol is a sugar-alcohol. Other six-carbon sugar alcohols found in nature include sorbitol (naturally present in pears; used in sugar-free chewing gum and diabetic foods) and mannitol (found in manna). Sugar alcohols such as sorbitol and mannitol are not actively absorbed in the intestinal tract, but are readily fermented by our intestinal bacteria. Because of this intestinal fermentation, sorbitol and mannitol fed in large amounts (several grams a day) can lead to gas, bloating, and even diarrhea. This is direct evidence that sugar alcohols such as inositol are readily degradable by microorganisms.

10. Safety information.

A Material Safety Data Sheet (MSDS) for inositol is provided in Appendix D (as well as in Appendix A). GRAS food ingredients are regulated by FDA (see 21 CFR 184.1370 in Appendix B) so a substance report from the National Institute of Environmental Health Studies does not exist.

11. Research information about the substance which includes comprehensive substance research reviews and research bibliographies, including reviews and bibliographies which present contrasting positions to those presented by the petitioner.

See the summaries of recent reviews in Item B-6, which consider the evidence for and against the essentiality of inositol, and conclude that it is prudent to ensure that infants receive as much inositol from infant formula as they would receive if they were human milk-fed. The full discussions from the LSRO reports of 1998 and 2002, which discussed the pros and cons of inositol addition to infant formula, are reproduced in Appendix E.

12. Petition Justification Statement

The nutrient inositol should be included on the National List for use as an ingredient in infant foods for several reasons.

First, as the NOSB was aware in 1995, the infant formula regulations existing at that time required the addition of inositol to infant formulas that would otherwise be devoid of this essential nutrient. This is why inositol was mentioned in the 1995 TAP Review and was mentioned in the NOSB's Recommendation.

Second, the NOSB knew at that time that nutrition knowledge would increase as the years passed and it was desirable not to be "limiting ourselves given future nutritional discoveries." The infant formula regulations existing in 1995, like the Infant Formula Act itself, reflected the 1976 recommendations of the Committee on Nutrition of the American Academy of Pediatrics,[6] which were last reviewed in 1985[7]. The most recent guidance on inositol addition to infant formula is that developed under FDA contract by the Life Sciences Research Office (LSRO) and published in 1998 and 2002. The emphasis of the scientific and pediatric communities in these newer reports reflects the growing endorsement of breast feeding as the preferred source of nutrients for infants and, for nutrients such as inositol, using the amounts found in human milk as a guide in establishing minimum and maximum levels in infant formulas. As the expert recommendations state, it is prudent that infants who are not human milk-fed receive as much inositol as human milk-fed infants do.

A third reason is that the current NOP position may either eliminate the organic choice for parents using infant formula or force parents to use nutritionally inferior human milk substitutes. The Organic Foods Protection Act (OFPA) of 1990, at 7 USC 6519(f), specifically indicates that nothing in the OFPA "shall alter the authority of . . . the Secretary of Health and Human Services under the Federal Food, Drug and Cosmetic Act." The Infant Formula Act of 1980 amended the Federal Food Drug, and Cosmetic Act to require the addition on inositol to certain infant formulas. The current NOP position would prohibit inositol addition to an organic infant formula. Adding inositol to the National List would avoid this dilemma.

As mentioned in Appendix E, most foodstuffs from both plant and animal sources are rich in free and phosphorylated forms of *myo*-inositol.

In plants, the predominant forms of *myo*-inositol are the phosphorylated phytates (phosphate salts of phytic acid), which are compounds known to form complexes with divalent cations (minerals like zinc and calcium).

[6] Commentary on Breast-Feeding and Infant Formulas, Including Proposed Standards for Formulas. Committee on Nutrition, American Academy of Pediatrics. Pediatrics 57(2): 278-285; 1976.
[7] Pediatric Nutrition Handbook, 2nd Edition. Committee on Nutrition, American Academy of Pediatrics, 1985. Appendix I, pp.356-7.

The digestive systems of most mammals cannot hydrolyze phytic acid[8], and hence neither its phosphorus nor its inositol is directly available.

Animal foods contain the free form of inositol. The concentration of *myo*-inositol in human milk is three to four times greater than that in cow milk. Human milk contains about 7% of its food energy as protein whereas cow milk contains 20% of its food energy as protein, or about three times as much protein as human milk, therefore cow milk must be diluted by a factor of two or more to reduce the protein level from 20% of total calories to a level less than 10% that is safe for the infant.[9] Thus the amount of inositol contributed by cows' milk to a milk-based infant formula is diluted to an even lower proportion of what is supplied by human milk.

A major nutritional reason for allowing continued inositol addition to infant formula is that infants fed some infant formulas have lower blood inositol levels than infants receiving human milk. Lung surfactant levels may be related to inositol levels in the blood. Supplementation of inositol to infants born preterm increases plasma inositol concentrations, reduces neonatal mortality, increases survival without chronic lung disease, and decreases the incidence and severity of retinopathy of prematurity, all findings consistent with inositol deficiency and consequent adverse effects in the infant born preterm. Infants of diabetic mothers also may be at increased risk for developing a deficiency in inositol and are at increased risk of neural tube defects, which may be in part the result of maternal hyperglycemia and subsequent deficiency of inositol in the developing offspring.[10]

Lastly, inositol is produced by hydrolysis of the phosphate groups of the natural substance phytic acid, hence making inositol a synthetic substance but also a bioavailable nutrient. Although phytic acid is the natural plant source of inositol, the mammalian digestive system is incapable of hydrolyzing the phosphate groups of phytic acid. Diets containing phytic acid are known to interfere with the absorption of essential mineral like calcium and magnesium, because the indigestible phytic acid complexes these essential minerals in the gut and make them unavailable to the body.

13. Confidential Business Information Statement

This petition contains no Confidential Business Information.

[8] Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride (1997) Institute of Medicine, Pp. 151-152.

[9] Milk proteins in infant nutrition: Development and manufacture of infant formula. R. C. Theuer. In W. Kaufmann, ed., Role of Milk Proteins in Human Nutrition. Verlag Th. Mann KG, Gelsenkirchen-Buer, Fed. Rep. Ger., 1983. Pp. 423-30.

[10] Groenen PM, Peer PG, Wevers RA, Swinkels DW, Franke B, Mariman EC, Steegers-Theunissen RP. Maternal myo-inositol, glucose, and zinc status is associated with the risk of offspring with spina bifida. Am J Obstet Gynecol. 2003;189:1713–9.

Appendices

Petition for addition to the National List of the substance INOSITOL, for use in infant formula products labeled as "organic."

Appendix A – Inositol Manufacturing

- U. S. Patents for Inositol Manufacture
  - U.S. Patent Number 2,112,553
  - U.S. Patent Number 2,414,365
- Inositol manufacturing procedure & MSDS - Tsuno Rice Fine Chemicals Co., Ltd.

Appendix B – U.S. Regulations and International Standards

- Inositol regulation
  - 21 CFR 184.1370
  - Food Chemicals Codex monograph for Inositol
- Infant Formula regulations
  - 21 CFR 107.10
  - 21 CFR 107.100(a)
- CODEX STAN 72-1981

Appendix C – Product Labels

Appendix D - MSDS

- Inositol Material Safety Data Sheet (MSDS) – Acros Organics

Appendix E - Comprehensive Substance Research Reviews

- Inositol discussion – 1998 LSRO report (Pp. 2127S-2129S)
- Inositol discussion – 2002 LSRO report (Pp. 1395S & 1446S-1449S only)

Patented Mar. 29, 1938 2,112,553

UNITED STATES PATENT OFFICE

2,112,553

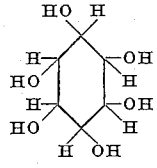
MANUFACTURE OF I-INOSITOL

Edward Bartow and William W. Walker,
Iowa City, Iowa

No Drawing. Application June 7, 1935, Serial No. 25,420. Renewed January 22, 1938

4 Claims. (Cl. 260—153)

This invention relates to improvement of the method for manufacturing i-inositol, hexahydroxycyclohexane, $(CHOH)_6$,



and has for its object, production of i-inositol more easily and at prices far below those now in existence in the chemical industry. The improvement is acomplished by the use of neutral, alkaline, or very dilute acid solution for hydrolysis or decomposition, by an improved method of extraction, and by a reduction in the number and amounts of chemical reagents required.

The compound i-inositol is used in bacteriology and has been tested for possible use in medicine. It can be nitrated and used as an explosive or it can possibly be acetylated and used as a rubber accelerator. It is prepared from a plant extract consisting chiefly of an impure calcium-magnesium salt of phytic acid, $C_6H_6O_6(PO(OH)_2)_6$, known as "phytin".

"Phytin" is obtained by extracting with dilute acid solution such as dilute hydrochloric (HCl) or sulfuric acid (H_2SO_4), various vegetable materials including seeds and grains such as corn, wheat, oats, etc. By this extraction in weak acid solution a variety of acid soluble constituents are obtained in a solution which can be separated by filtration or other suitable mechanical treatment.

From this liquid, a portion of the acid soluble material, including insoluble salts and other compounds, is precipitated by the addition of an alkali reagent; for example, $Ca(OH)_2$, NaOH, Na_2CO_3, $(NH_4)_2CO_3$, etc. until the neutral point of the solution, approximately pH 7.0 is reached. This insoluble precipitate, known as "phytin" can be removed by filtration, sedimentation or other suitable mechanical means.

The calcium-magnesium content is variable depending on the plan source and the alkaline reagent used for the precipitation. The "phytin" is an impure phytic acid salt, containing other compounds.

Heretofore in the preparation of i-inositol i. e., inactive inositol from the impure "phytin" the "phytin" has been decomposed or hydrolyzed by strong sulfuric acid (H_2SO_4) solution. The hydrolysis has been carried out in a sealed tube or in open vessels, in the latter case using the higher acid concentrations. The majority of workers have used approximately 30% sulfuric acid solution and have hydrolyzed the mixture in a steam digester or autoclave with varying steam pressures for varying intervals of time.

In reactions as heretofore carried out using strong sulfuric acid in excess there are formed precipitates of calcium or magnesium sulfate, the solution containing sulfuric and phosphoric acids in addition to the desired i-inositol. It has been necessary to eliminate these acids by precipitation with alkaline reagents such as a barium compound followed by carbonation to remove the barium.

By the process of the present invention the need for these additional chemicals is entirely or practically eliminated. According to this process it has been found that the hydrolysis can be accomplished without the addition of any acid and by merely mixing the "phytin" with varying quantities of water under pressure; as for example, mixing "phytin" one part and water 1 to 100 parts, to form at least a thin paste, followed by hydrolyzing the mixture in a closed vessel with steam pressure of from 1 to 200 pounds for intervals of from 1 to 50 hours the time required being correspondingly less for higher pressures. It has been found further that hydrolysis can be accomplished at a higher pH even, by alkaline solutions such as lime water $Ca(OH)_2xH_2O$, or baryta water $Ba(OH)_2xH_2O$ of different strengths, as well as by dilute acid solutions of less than 10% concentration. The same pressures and time intervals as in the acid hydrolysis will produce good yields of i-inositol.

Hydrolysis of "phytin" breaks the complex molecule into free i-inositol and calcium and magnesium phosphates, $Ca_3(PO_4)_2$, $CaHPO_4$, $Mg_3(PO_4)_2$, $MgHPO_4$, etc. These calcium and magnesium phosphates are sparingly soluble in water and settle as insoluble sludges, when the solution is alkaline or made alkaline by a precipitating agent such as $Ca(OH)_2$, CaO, $Ba(OH)_2$, BaO, etc. The i-inositol is in solution or adsorbed on the flocculent insoluble fraction or sludge.

Although filtration and washing on the filter can be used, it is now found more satisfactory to remove the hydrolysis mixture from the autoclave and dilute it with water. This mixture is then heated to the boiling point either with steam under pressure or with outside heat and the suspended sludge is vigorously agitated, with the result that more complete removal of the i-inositol is obtained. The solution containing the i-inositol can be given a primary separation as by de-

cantation of supernatant clear liquid from the sludge. More water is then added to the separated sludge for a supplementary or more complete washing while being similarly heated and agitated, and the clear liquid again decanted. Repetition of this procedure, as needed, removes the i-inositol from the sludge formed.

Inactive inositol may be prepared from starch factory steep water which is the liquid in which corn is steeped to soften the covering of the corn kernel and to thoroughly soften the entire kernel. It contains approximately 1% sulfurous acid (H_2SO_3) in solution. A typical example of such treatment consists in adding to the acid steep water, lime $Ca(OH)_2$ or CaO to approximate neutrality, or to a pH of 6.0 to 8.0, at which range the insoluble "phytin" is precipitated. This precipitate of impure "phytin" or calcium phytate is removed by suitable means, as stated before, and may be mixed with (1) 1 to 10% acid solution; or (2) diluted with water; or (3) the solution may be made alkaline. This alkaline or neutral or acid mixture is placed in a suitable container in an autoclave or steam digester, and the steam turned on whereupon the reaction is allowed to proceed as long as desired. The autoclave in which the mixture has been placed may be heated by generating steam therein, by means of an electric heater, or by suitable heat from outside. A pressure of from 1 to 200 pounds steam for 1 to 18 hours may be used, the time required being correspondingly less for higher pressures. A suitable pressure is 80 pounds. The time expected for 80 pounds is three hours.

After hydrolysis or decomposition is complete, pressure is released, the autoclave cooled, the mixture removed, diluted, and made alkaline with $Ca(OH)_2$, $Ba(OH)_2$ etc., brought to boiling, thoroughly agitated with steam, the insoluble sludge allowed to settle, and the supernatant liquid removed by decantation, siphoning or filtration. The supernatant liquid is concentrated in an open vessel, or in vacuum, to remove the precipitating inorganic impurities as calcium carbonate ($CaCO_3$), magnesium carbonate ($MgCO_3$), etc. The liquid is concentrated until it becomes thick and syrupy. The concentrated solution is filtered, cooled, and agitated by a suitable mechanical means to precipitate i-inositol. The i-inositol is removed by filtration, the mother liquor concentrated, and the process repeated until the solution becomes too thick to filter advantageously. A filter press may be employed to remove further quantities of i-inositol, or the thick residue may be diluted with a reagent in which i-inositol is insoluble; as for example, acetic acid (CH_3COOH) and alcohol-acetic acid (C_2H_5OH, CH_3COOH etc.). On cooling and stirring the solution, additional i-inositol, etc., results and can be removed by filtration or other mechanical means. The i-inositol may be recrystallized by dissolving the crude product in boiling water, and reprecipitated by cooling and stirring. The final crystallization from a hot water solution to which an equal volume of alcohol is added with cooling and stirring, gives a purer product.

It will be understood from this patent that we do not limit ourselves to any specific acid concentration below 10% or to any specific acid; as for example, hydrochloric (HCl), sulfuric (H_2SO_4) phosphoric (H_3PO_4) etc. We wish to include the neutral solution and all strengths of alkaline solution up to 25% alkali; for example, lime CaO, $Ca(OH)_2$, BaO, $Ba(OH)_2$, etc. are suitable solutions in which phytin may be satisfactorily hydrolyzed. It will be understood that any method of heating or agitating the mixture by steam or other heated vapors to remove the adsorbed i-inositol from the insoluble sludges are included in this method. It will be understood that any application of decantation or siphoning or other similar mechanical means to remove the supernatant liquid are included in our method. It will be further understood that we do not limit ourselves to the use of any particular type or size of autoclave, any definite steam or vapor pressure, or any definite time intervals for the hydrolysis reaction.

We claim:

1. The method for the manufacture of i-inositol by the decomposition of phytin in which the decomposition is effected in alkaline solution of a concentration below that corresponding to 25% alkalinity.

2. The method for the manufacture of i-inositol by the decomposition of salts of phytic acid in which the decomposition is effected in alkaline solution below 25%.

3. The process for the manufacture of i-inositol from phytic acid salts which comprises decomposing the salts by means of steam and pressure in an alkaline solution of alkalinity less than 25%, carrying out a primary separation of the resultant solution and the precipitate, adding water to the separated precipitate, heating and agitating to remove adsorbed i-inositol from the precipitate, and carrying out a supplementary separation of the precipitate from the solution.

4. The process for the manufacture of directly separable i-inositol from phytin prepared directly from vegetable materials which comprises decomposing the phytin by means of steam and pressure in a solution of approximately 0 to 25% alkalinity, carrying out a primary separation of the resultant solution and the precipitate, adding water to the separated precipitate, heating and agitating to remove adsorbed i-inositol from the precipitate, and carrying out a supplementary separation of the precipitate from the solution.

EDWARD BARTOW.
WILLIAM W. WALKER.

Patented Jan. 14, 1947

2,414,365

UNITED STATES PATENT OFFICE

2,414,365

PRODUCTION OF i-INOSITOL

Milton Elkin, Dorchester, Mass., and Carl M. Meadows, Nanuet, N. Y., assignors, by mesne assignments, to American Cyanamid Company, New York, N. Y., a corporation of Maine

No Drawing. Application May 28, 1942, Serial No. 444,926

6 Claims. (Cl. 260—631)

1

This invention relates to the production of i-inositol (inactive inositol) and more particularly relates to an improved method for obtaining i-inositol by hydrolyzing salts of phytic acid.

In the past it has been proposed to isolate i-inositol from calcium phytate using acid, alkaline, or neutral hydrolysis. (U. S. Patent No. 2,112,553 and Industrial and Engineering Chemistry, 20, page 300, 1938.) These prior art processes have not been entirely satisfactory in that they required the use of rather strongly acid solutions or that the hydrolysis be carried out at greatly elevated temperatures and pressures.

It is an advantage of the present invention that an improved method for hydrolyzing salts of phytic acid is provided which permits the use of lower temperatures and pressures than the previously known methods. It is also an advantage of this invention that complete hydrolysis of phytic acid salts and a higher over-all recovery of i-inositol is obtained under practical operating conditions. It is a further advantage of our invention that the hydrolysis of phytates in near neutral and acidic solutions are catalyzed by ammonium salts.

In carrying out our invention phytates are subjected to a hydrolytic treatment in the presence of an ammonium salt. In general an aqueous solution or suspension of a phytate, which solution may be nearly neutral or acidic, has added thereto an ammonium salt after which the solution is autoclaved for from 1 to 15 hours at from about 10 to 20 pounds pressure.

2

The process will be further illustrated in conjunction with the following specific examples. It should be understood, however, that the examples are given for the purpose of illustration and not by way of limitation.

EXAMPLE 1

Hydrolysis in a Near Neutral Medium

Ten gram samples of phytates in near neutral solutions, prepared as indicated in the table below were hydrolyzed by autoclaving for 15 hours at 17 pounds pressure. The initial inorganic phosphorus content before hydrolysis and the final inorganic phosphorus content after hydrolysis were determined in order to calculate the percentage hydrolysis.

Table I

No.	Sample in 50 cc. H_2O	$(NH_4)_2SO_4$	pH	Initial inorganic phosphorus	Final inorganic phosphorus	Total phosphorus	Per cent hydrolysis
		Gms.		*Mg.*	*Mg.*	*Mg.*	
1A	10 g. NH_4 phytate	0	6.4	33	495	1,076	46.00
2A	do	5	6.35	33	588	1,076	54.64
3A	do	10	6.44	33	691	1,076	64.22
1B	10 g. Na phytate	0	6.88	35	610	1,150	53.02
2B	do	5	6.89	35	625	1,150	54.30
3B	do	10	6.90	35	654	1,150	56.82

EXAMPLE 2

Hydrolysis in an Acid Medium

The experiments outlined in Table II follow the same procedure as those of Example 1 except that the autoclave time was varied and that the hydrolysis was carried out in an acid medium.

Table II

No.	Time of autoclaving	Sample in 50 cc. H_2O	$(NH_4)_2SO_4$	pH	Initial inorganic phosphorus	Final inorganic phosphorus	Total phosphorus	Per cent hydrolysis
	Hrs.		*Gms.*		*Mg.*	*Mg.*	*Mg.*	
1	8	10 gm. NH_4 phytate	0	3.18	33	955	1,076	88.1
2	8	do	10	3.18	33	1,087	1,076	100.8
1A	4	do	0	3.03	33	909	1,076	83.7
2A	4	do	10	3.05	33	1,065	1,076	98.1
1B	2½	do	0	3.45	33	564	1,076	50.8
2B	2½	do	10	3.47	33	804	1,076	73.7

The data in the above table indicate that the sample (2) containing ammonium sulfate was completely hydrolyzed, showing a 12% improvement over the sample (1) containing no ammonium sulfate. This degree of superiority is accounted for without taking into consideration the possibility of complete hydrolysis having occurred in less than eight hours. It is particularly significant therefore to note in the experiments in which the samples (1A and 2A, 1B and 2B)

were autoclaved for four hours and 2½ hours the difference in hydrolysis increased to 14.4% and 22.9%, respectively.

In the foregoing specific examples ammonium and sodium phytates were employed as the starting materials. Instead of these phytates various other phytates may be employed, including calcium phytate, barium phytate, magnesium phytate, potassium phytate, iron phytate, strontium phytate, manganese phytate, hexa-copper phytate, octa-silver phytate, or any other metal salt of phytic acid.

We prefer to use ammonium sulfate as the ammonium salt for catalyzing the hydrolysis of phytates because of its cheapness and ready availability. It should be distinctly understood, however, that ammonium salts, such as ammonium chloride, ammonium nitrate, ammonium acetate, ammonium phosphate, or other ammonium acid salts, may be employed in our process for catalyzing the hydrolytic splitting of phytates into i-inositol and phosphates or phosphoric acid.

The time of autoclaving, the pressure, and the pH of the phytate solution or suspension may be varied within reasonable limits from those specifically illustrated. The optimum conditions may be determined experimentally for any particular phytate, and the hydrolysis then carried out under the most economical conditions. In general, the time of autoclaving may be varied from one to fifteen hours and the pressures from 15 to 20 pounds per square inch. The pH of the starting solution may be varied from about 6.90 to about 2.5, the best results usually being obtained when the solution at the beginning has a pH of about 3.

The crude phytic acid salts obtained from steep waters produced in the manufacture of corn starch are amenable to our hydrolysis process; and this is of great commercial importance because one of the most abundant sources of phytin is from this steep water obtained as a by-product in the production of corn starch. As pointed out previously, the ratio of ammonium salt to phytate may be varied to permit operations employing a wide range of temperatures, pressures, and times, to give satisfactory hydrolysis of the phytates. In most instances rather mild conditions wherein the pH of the solutions has been adjusted to 3.0 to about 3.5 result in complete hydrolysis in an economical period of time. While the ratio of phytate to ammonium salt is not particularly critical, we have found that with commercially available crude phytates the concentration of ammonium salt should be not less than about 1 part per five parts of water and that the phytate suspended in the solution be not less than about one part per five parts water. This suspension should then be adjusted to an acidity of approximately pH 3 and autoclaved at about 15 pounds pressure for fifteen hours or such time as is shown by phosphorus determinations to be required for complete hydrolysis. The pH adjustments of the suspension may be made utilizing any satisfactory acid and any satisfactory base. We have found that sulfuric acid and sodium hydroxide are entirely satisfactory for making the pH adjustments.

The i-inositol prepared in accordance with our process may be recovered from the hydrolysis mixture by any satisfactory method. We have found that the i-inositol may be isolated in good

yields by a process which comprises diluting the solution with an equal volume of water and adding calcium oxide with vigorous stirring to distinct alkalinity. The resultant suspension is treated with decolorizing charcoal and filtered hot. If desired, the solid residue may be resuspended in a volume of water equal to the filtrate, stirred vigorously, while heating for about thirty minutes. The solution is then filtered and the two filtrates combined and concentrated to about one-fifth to one-tenth of the original volume. An equal volume of 95% ethyl alcohol is added to this concentrate and filtered, the precipitate being washed with 50% alcohol. This alcoholic filtrate is concentrated to a syrup and diluted with four to five volumes of glacial acetic acid, after which crystallization is allowed to proceed in a cold room. The precipitated i-inositol is washed with glacial acetic acid and recrystallized from warm 50% acetic acid.

It is obvious that the above description and examples are intended to be illustrative only and that they may be varied or modified to a considerable extent without departing from the spirit of the invention or sacrificing the advantages thereof. We do not, therefore, intend to limit ourselves to the specific embodiments herein set forth except as indicated in the appended claims.

What we claim is:

1. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises carrying the hydrolysis out by heating a phytate in the presence of an ammonium acid salt in an aqueous solution having an acidic reaction.

2. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises hydrolyzing a phytate in an aqueous solution having a pH of from about 2.5 to 6.9 and containing an ammonium acid salt by subjecting said phytate to a heat treatment at from about 15 to 20 pounds pressure.

3. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises subjecting an aqueous solution of a phytate and an ammonium salt, wherein the pH of said solution falls within the range of about 3.0 to about 6.9, to a heat treatment at from about 15 to 20 pounds pressure.

4. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises subjecting an aqueous solution of a phytate and ammonium sulfate, wherein the pH of said solution falls within the range of about 3.0 to about 6.9, to a heat treatment at from about 15 to 20 pounds pressure.

5. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises subjecting an aqueous solution of sodium phytate and ammonium sulfate, wherein the pH of said solution falls within the range of about 3.0 to about 6.9, to a heat treatment at from about 15 to 20 pounds pressure.

6. In the method for the preparation of i-inositol by hydrolysis of phytates the improvement which comprises subjecting an aqueous solution of ammonium phytate and ammonium sulfate, wherein the pH of said solution falls within the range of about 3.0 to about 6.9, to a heat treatment at from about 15 to 20 pounds pressure.

MILTON ELKIN.
CARL M. MEADOWS.

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Produion and Process Control

a) Raw Material : Defatted Rice Bran (Attached sheet 5)

b) Manufacturing Process : (INOSITOL Manufacturing Flow Chart)

Reaction:

$$C_6H_6O_{24}P_6Mg_{3\sim4}Ca_{2\sim1}K_2 \text{ (Rice Bran Phytin)} \xrightarrow{\text{Hydrolysis}} C_6H_6O_6 \text{ (INOSITOL)}$$

Process chart:

Defatted Rice Bran
↓
Extraction (pH 3.0～4.0)
↓
Separation → Processed Rice Bran
↓
Filtrated liquid
↓
Neutralization (pH 7～11)
↓
Filtration → Waste liquid
↓
Hydrolysis (190～230℃ 20～28kg/cm²)
↓
Fertilizer
↓
Filtration → Calcium Phosphate Di-Basic
↓
Filtrated liquid
↓
Decolorization (Ion Exchange Resin - Decolorization rate: 70% or more)
↓
Demineralization (Ion Exchange Resin -Applied liquid: 30μs or less)
↓
Concentration (Multiple Applicable can - Concentration: 25～35%)
↓
Crystallization
↓
Drying (85℃ , 1 hour or more)
↓
Shifter (18～80 Mesh)or Pulverize
↓
Filling
↓
Product (Sampling)
↓
Storing at Warehouse

MATERIAL SAFETY DATA SHEET

NAME: Inositol PRODUCT NUMBER: 090200-BMS

DATE REVISED: July 11, 2006 SUPERCEDES: June 2000

SELTZER INGREDIENTS
5927 GEIGER COURT
CARLSBAD, CA 92008-7305
760/438-0089
760/438-0336 FAX

I. PRODUCT INFORMATION

TRADE NAMES/SYNONYMS: Inositol

CHEMICAL NAME: myo-Inositol, hyxahydroxycyclohexane

CAS NUMBER: 87-89-8

CHEMICAL FORMULA: C6H12O6

II. SUMMARY OF HAZARDS

None.

III. HAZARDOUS COMPONENTS

None.

IV. CHEMICAL AND PHYSICAL PROPERTIES

BOILING POINT: N/A

MELTING POINT: 224-227 Deg. C

SOL. IN WATER: 14 g/100 ml, 25 Deg. C

pH: N/A

VAPOR PRESSURE: N/A

VAPOR DENSITY: N/A

SPECIFIC GRAVITY: N/A

EVAPORATION RATE: N/A

APPEARANCE/ODOR: White crystalline powder.

V. HEALTH HAZARD DATA & FIRST AID PROCEDURES

THRESHOLD LIMIT VALUE: Non-Toxic

EYE CONTACT: Rinse immediately with water. Seek medical advice if irritation occurs.

SKIN CONTACT: Wash with soap and water.

INHALATION: Remove to fresh air. Seek medical attention if discomfort occurs.

INGESTION: Seek medical advising if discomfort or illness occurs. Not expected to be hazard in reasonable amounts.

VI. EXPOSURE CONTROL MEASURES

EYE PROTECTION: Goggles

PROTECTIVE GLOVES: Chemical resistant gloves

RESPIRATORY PROTECTION: OSHA approved mask.

OTHER PROTECTION: Use good manufacturing practices.

VII. FIRE AND EXPLOSION HAZARD DATA

FLASH POINT (METHOD USED): N/A

FLAMMABLE LIMITS LOWER: UPPER:

EXTINGUISHING MEDIA: water,

FIRE FIGHTING INSTRUCTIONS: normal procedure

UNUSUAL FIRE AND EXPLOSION HAZARDS: none

VIII. REACTIVITY DATA

STABILITY: Stable under normal conditions.

INCOMPATIBILITY: open air and sunlight

HAZARDOUS PRODUCTS OF DECOMPOSITION: none

HAZARDOUS POLYMERIZATION: none

IX. ENVIRONMENTAL AND DISPOSAL INFORMATION

ACTION TO TAKE FOR SPILLS/LEAKS: Sweep up and dispose.

DISPOSAL METHOD: Dispose of in accordance with local, state, and federal regulations.

X. PRECAUTIONS FOR SAFE HANDLING, STORAGE AND USE

Cool, dry storage. Use good manufacturing practices.

XI. SHIPPING INFORMATION

Not regulated for shipping purposes.

XII. ADDITIONAL INFORMATION

None.

NOTICE

The data contained herein is based on information that Seltzer Ingredients believes to be reliable, but no expressed or implied warranty is made with regard to the accuracy of such data or its suitability for a given situation. Such data relates only to the specific product described and not to such product in combination with any other product and no agent of Seltzer Ingredients is authorized to vary any of such data. Seltzer Ingredients and its agent disclaim all liability for any actions taken or foregone on reliance upon such data.

(d) Residual hydrogen peroxide is removed by appropriate physical and chemical means during the processing of food where it has been used according to paragraph (c) of this section.

(e) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[46 FR 44439, Sept. 4, 1981, as amended at 51 FR 27172, July 30, 1986]

§ 184.1370 Inositol.

(a) Inositol, or myo-inositol ($C_6H_{12}O_6$, CAS Reg. No. 87–89–8), is *cis*-1,2,3,5-*trans*-4,6-cyclohexanehexol. It occurs naturally and is prepared from an aqueous (0.2 percent sulfur dioxide) extract of corn kernels by precipitation and hydrolysis of crude phytate.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 150, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, 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*.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitations other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as a nutrient supplement as defined in § 170.3(o)(20) of this chapter.

(2) The ingredient is used in special dietary foods as defined in part 105 of this chapter at levels not to exceed current good manufacturing practice. It may also be used in infant formula in accordance with section 412(g) of the Act, or with regulations promulgated under section 412(a)(2) of the Act.

(d) Prior sanctions for this ingredient different from the uses established by this section do not exist or have been waived.

[47 FR 38278, Aug. 31, 1982]

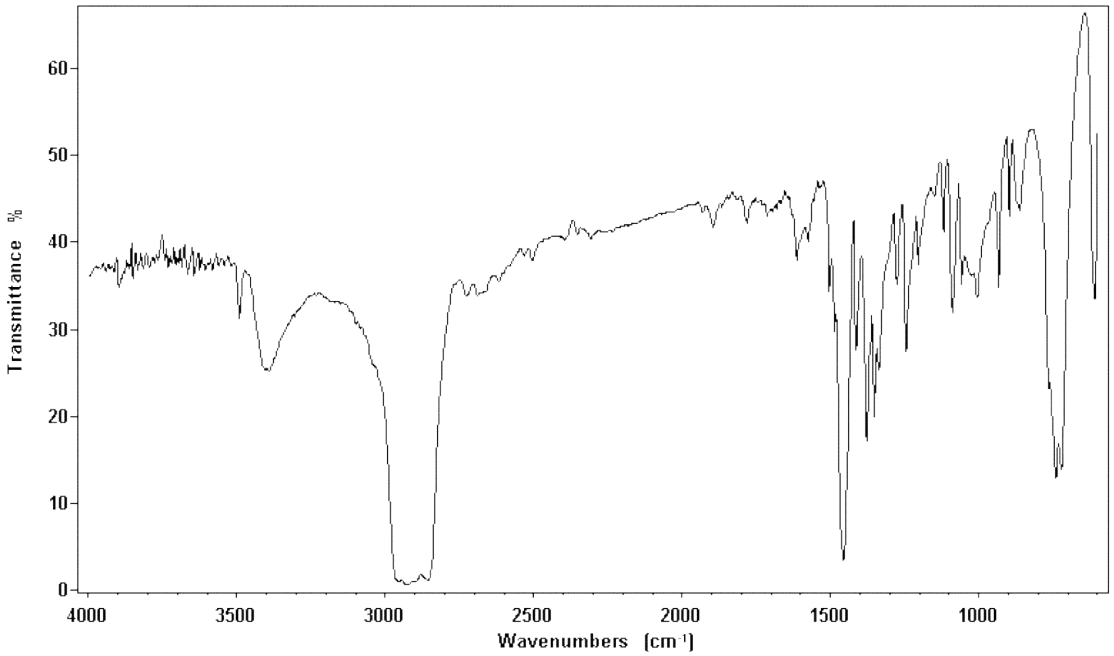
§ 184.1372 Insoluble glucose isomerase enzyme preparations.

(a) Insoluble glucose isomerase enzyme preparations are used in the production of high fructose corn syrup described in § 184.1866. They are derived from recognized species of precisely classified nonpathogenic and nontoxicogenic microorganisms, including *Streptomyces rubiginosus*, *Actinoplanes missouriensis*, *Streptomyces olivaceus*, *Streptomyces olivochromogenes*, and *Bacillus coagulans*, that have been grown in a pure culture fermentation that produces no antibiotics. They are fixed (rendered insoluble) for batch production with GRAS ingredients or may be fixed for further immobilization with either GRAS ingredients or materials approved under § 173.357 of this chapter.

(b) The ingredient meets the general and additional requirements for enzyme preparations in the Food Chemicals Codex, 3d Ed. (1981), p. 107, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, 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*.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme, as defined in § 170.3(o)(9) of this chapter, to convert glucose to fructose.

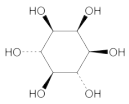


Indole (Mineral Oil Mull)

Inositol

First Published: Prior to FCC 6

1,2,3,5/4,6-Cyclohexanehexol
i-Inositol
meso-Inositol
myo-Inositol



$C_6H_{12}O_6$ Formula wt 180.16
CAS: [87-89-8]

DESCRIPTION

Inositol occurs as fine, white crystals or as a white, crystalline powder. Its solutions are neutral to litmus. It is optically inactive. It is stable in air. One g is soluble in 6 mL of water. It is slightly soluble in alcohol, and is insoluble in ether and in chloroform.

Function: Nutrient

Packaging and Storage: Store in well-closed containers.

IDENTIFICATION

- **A. Procedure**

  Sample solution: 20 mg/mL

  Anlaysis: Add 6 mL of nitric acid to 1 mL of *Sample solution* in a porcelain evaporating dish and evaporate to dryness on a water bath. Dissolve the residue in 1 mL of water, add 0.5 mL of a 100 mg/mL solution of strontium acetate, and again evaporate to dryness on a steam bath.

  Acceptance criteria: A violet color appears.

- **B. Melting Range or Temperature,** Appendix IIB

  Sample: The inositol hexaacetate residue obtained from the *Assay* (below)

  Acceptance criteria: Between 212° and 216°

ASSAY

- **Procedure**

  Sample: 200 mg, previously dried

  Analysis: Transfer the *Sample* to a 250-mL beaker, add 5 mL of a 1:50 mixture of 2 N sulfuric acid:acetic anhydride, and cover the beaker with a watch glass. Heat on a steam bath for 20 min, then chill in an ice bath, and add 100 mL of water. Boil for 20 min, allow to cool, and transfer quantitatively, with the aid of a little water, to a 250-mL separatory funnel. Extract the solution with six successive 30-, 25-, 20-, 15-, 10-, and 10-mL portions of chloroform, using the solvent to rinse the original flask. Collect the chloroform extracts in a second 250-mL separatory funnel, and wash the combined extracts with 10 mL of water. Transfer the chloroform extracts through a funnel containing a pledget of cotton into a 150-mL tared Soxhlet flask. Wash the separatory funnel and funnel with 10 mL of chloroform, and add to the combined extracts. Evaporate to dryness on a steam bath, dry in an oven at 105° for 1 h, cool in a desiccator, and weigh. [NOTE—Save this residue for use in *Identification test B* (above).] The weight of the inositol hexaacetate obtained, multiplied by 0.4167, represents the equivalent of $C_6H_{12}O_6$.

Acceptance criteria: NLT 97.0% $C_6H_{12}O_6$, on the dried basis

IMPURITIES

Inorganic Impurities

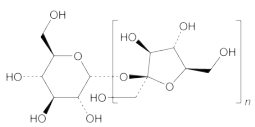
- **CALCIUM**
  Sample solution: 100 mg/mL
  Analysis: Add 1 mL of ammonium oxalate TS to 10 mL of the *Sample solution*.
  Acceptance criteria: The resulting solution remains clear for at least 1 min.
- **CHLORIDE,** *Chloride and Sulfate Limit Tests***,** *Chloride Limit Test,* Appendix IIIB
  Sample: 400 mg
  Control: 20 µg of chloride (2.0 mL of *Standard Chloride Solution*)
  Acceptance criteria: Any turbidity produced by the *Sample* does not exceed that shown in the *Control* (NMT 0.005%).
- **LEAD,** *Lead Limit Test,* Appendix IIIB
  Sample: Prepare as directed for organic compounds.
  Control: 4 µg Pb (4 mL of *Diluted Standard Lead Solution*)
  Acceptance criteria: NMT 4 mg/kg
- **SULFATE,** *Chloride and Sulfate Limit Tests, Chloride Limit Test,* Appendix IIIB
  Sample: 5 g
  Control: 300 µg of sulfate (30 mL of *Standard Sulfate Solution*)
  Acceptance criteria: Any turbidity produced by the *Sample* does not exceed that in the *Control* (NMT 0.006%).

SPECIFIC TESTS

- **LOSS ON DRYING,** Appendix IIC**:** 105° for 4 h
  Acceptance criteria: NMT 0.5%
- **MELTING RANGE OR TEMPERATURE,** Appendix IIB
  Acceptance criteria: Between 224° and 227°
- **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC
  Sample: 2 g
  Acceptance criteria: NMT 0.1%

Inulin

First Published: FCC 6



CAS: [9005-80-5]

DESCRIPTION

Inulin occurs as a white powder. It is an indigestible plant fructan found in members of the *Compositae* family. Commercial production is by extraction from the roots of *Cichorium intybus* Lin. (chicory). It is a mixture composed of polymers of *β*-2,1-linked fructose residues mostly linked to a terminal glucose residue. The degree of polymerization in the mixture varies between 3 and 60, with the longer-chain polymers being predominant. It is very soluble in hot water, slightly soluble in cold water, and almost insoluble in most organic solvents.

Function: Source of dietary fiber; binder; bulking agent; texturizer

Packaging and Storage: Store in well-closed containers.

IDENTIFICATION

- **PROCEDURE**
  Mobile phase: Water
  Acetate buffer (pH 4.5 ± 0.05): 0.044 M sodium acetate and 0.056 M acetic acid
  Standard solution: 5 mg/mL fructose, 1 mg/mL glucose, and 1 mg/mL sucrose
  Sample stock solution: Transfer 1 to 1.5 g of sample, into a 100-mL volumetric flask. Dissolve the sample in hot (>80°) water and allow the solution to cool before diluting to volume.
  Digested sample solution: Transfer 10 mL of *Acetate buffer* and 10 mL of the *Sample stock solution* into a 25-mL volumetric flask. Add 150 units of Fructozyme SP230 enzyme (Novozymes, Denmark), or equivalent. Digest for 30 min at 60°, cool, and dilute to volume with water.
  Chromatographic system, Appendix IIA
  Mode: High-performance liquid chromatography
  Detector: Refractive index
  Column: Gel filtration column for molecular weight range up to 5000 Da (Shodex KS-802, Showa Denko, K.K., Tokyo, Japan, or equivalent)
  Temperature
  Column: 50°
  Detector: 35°–40°
  Flow rate: 1 mL/min
  Injection volume: 20 µL
  Sample loop: 20 µL
  Analysis: Separately inject the *Digested sample solution* and the *Standard solution* into the chromatograph and record the chromatograms. Determine the percentage of fructose and the percentage of glucose in the *Digested sample solution* using the following formula:

$$\text{Result} = 100(C_{ST} \times A_{SA})/(A_{ST} \times W)$$

C_{ST} = concentration of fructose or glucose in the *Standard solution* (mg/100 mL)
A_{SA} = area of the corresponding sugar peak in the chromatogram of the *Sample solution*
A_{ST} = area of the corresponding sugar peak in the chromatogram of the *Standard solution*
W = weight of sample, in g, contained in each 100 mL of the *Sample stock solution*

Correct the percent fructose and percent glucose results for the mono- and disaccharide content (obtained in the *Assay* below), and for moisture.

by telephone, to the Director of the appropriate Food and Drug Administration district office specified in part 5, subpart M of this chapter. After normal business hours (8 a.m. to 4:30 p.m.) the FDA emergency number, 301–443–1240, shall be used. The manufacturer shall send a followup written confirmation to the Center for Food Safety and Applied Nutrition (HFS–605), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, and to the appropriate Food and Drug Administration district office specified in part 5, subpart M of this chapter.

[47 FR 17025, Apr. 20, 1982, as amended at 54 FR 24891, June 12, 1989; 61 FR 14479, Apr. 2, 1996; 66 FR 17358, Mar. 30, 2001; 66 FR 56035, Nov. 6, 2001; 69 FR 17291, Apr. 2, 2004]

PART 107—INFANT FORMULA

Subpart A—General Provisions

Subpart B—Labeling

Subpart C—Exempt Infant Formulas

Subpart D—Nutrient Requirements

Subpart E—Infant Formula Recalls

AUTHORITY: 21 U.S.C. 321, 343, 350a, 371.

SOURCE: 50 FR 1840, Jan. 14, 1985, unless otherwise noted.

Subpart A—General Provisions

§ 107.3 Definitions.

The following definitions shall apply, in addition to the definitions contained in section 201 of the Federal Food, Drug, and Cosmetic Act (the act):

Exempt formula. An exempt infant formula is an infant formula intended for commercial or charitable distribution that is represented and labeled for use by infants who have inborn errors of metabolism or low birth weight, or who otherwise have unusual medical or dietary problems.

Manufacturer. A manufacturer is a person who prepares, reconstitutes, or otherwise changes the physical or chemical characteristics of an infant formula or packages the infant formula in containers for distribution.

References. References in this part to regulatory sections of the Code of Federal Regulations are to chapter I of title 21, unless otherwise noted.

[50 FR 48186, Nov. 22, 1985]

Subpart B—Labeling

§ 107.10 Nutrient information.

(a) The labeling of infant formulas, as defined in section 201(aa) of the Federal Food, Drug, and Cosmetic Act, shall bear in the order given, in the units specified, and in tabular format, the following information regarding the product as prepared in accordance with label directions for infant consumption:

(1) A statement of the number of fluid ounces supplying 100 kilocalories (in case of food label statements, a kilocalorie is represented by the word ''Calorie''); and

(2) A statement of the amount of each of the following nutrients supplied by 100 kilocalories:

Nutrients	Unit of measurement
Protein	Grams.
Fat	Do.
Carbohydrate	Do.
Water	Do.
Linoleic acid	Milligrams.
Vitamins:	
Vitamin A	International units.
Vitamin D	Do.
Vitamin E	Do.
Vitamin K	Micrograms.
Thiamine (Vitamin B_1)	Do.
Riboflavin (Vitamin B_2	Do.

Nutrients	Unit of measurement
Vitamin B_6	Do.
Vitamin B_{12}	Do.
Niacin	Do.
Folic acid (Folacin)	Do.
Pantothenic acid	Do.
Biotin	Do.
Vitamin C (Ascorbic acid)	Milligrams.
Choline	Do.
Inositol	Do.
Minerals:	
Calcium	Milligrams.
Phosphorus	Do.
Magnesium	Do.
Iron	Do.
Zinc	Do.
Manganese	Micrograms.
Copper	Do.
Iodine	Do.
Sodium	Milligrams.
Potassium	Do.
Chloride	Do.

(b) In addition the following apply:

(1) Vitamin A content may also be declared on the label in units of microgram retinol equivalents, vitamin D content in units of micrograms cholecalciferol, vitamin E content in units of milligram alpha-tocopherol equivalents, and sodium, potassium, and chloride content in units of millimoles, micromoles, or milliequivalents. When these declarations are made they shall appear in parentheses immediately following the declarations in International Units for vitamins A, D, and E, and immediately following the declarations in milligrams for sodium, potassium, and chloride.

(2) Biotin, choline, and inositol content shall be declared except when they are not added to milk-based infant formulas.

(3) Each of the listed nutrients, and the caloric density, may also be declared on the label on other bases, such as per 100 milliliters or per liter, as prepared for infant consumption.

(4) One of the following statements shall appear on the principal display panel, as appropriate:

(i) The statement ''Infant Formula With Iron'', or a similar statement, if the product contains 1 milligram or more of iron in a quantity of product that supplies 100 kilocalories when prepared in accordance with label directions for infant consumption.

(ii) The statement ''Additional Iron May Be Necessary'', or a similar statement, if the product contains less than 1 milligram of iron in a quantity of product that supplies 100 kilocalories when prepared in accordance with label directions for infant consumption.

(5) Any additional vitamin may be declared at the bottom of the vitamin list and any additional minerals may be declared between iodine and sodium, provided that any additionally declared nutrient (i) has been identified as essential by the National Academy of Sciences through its development of a recommended dietary allowance or an estimated safe and adequate daily dietary intake range, or has been identified as essential by the Food and Drug Administration through a FEDERAL REGISTER publication or establishment of a U.S. Recommended Daily Allowance, and (ii) is provided at a level considered in these publications as having biological significance, when these levels are known.

[50 FR 1840, Jan. 14, 1985, as amended at 67 FR 9585, Mar. 4, 2002]

§ 107.20 Directions for use.

In addition to the applicable labeling requirements in parts 101 and 105 of this chapter, the product label shall bear:

(a) Under the heading ''Directions For Preparation and Use'', directions for:

(1) Storage of infant formula before and after the container has been opened, including a statement indicating that prolonged storage at excessive temperatures should be avoided;

(2) Agitating liquid infant formula before opening the container, such as ''Shake Well Before Opening'';

(3) ''Sterilization'' of water, bottle, and nipples when necessary for preparing infant formula for use;

(4) Dilution of infant formula, when appropriate. Directions for powdered infant formula shall contain the weight and volume of powdered formula to be reconstituted.

(b) In close proximity to the ''Directions for Preparation and Use'' a pictogram depicting the major steps for preparation of that infant formula, such as (for a concentrated formula):

may exist and so notifies the manufacturer, withdrawal of a product's exempt status shall be effective on the date of receipt of notification from the Director of the Center for Food Safety and Applied Nutrition. Additional or modified requirements, or the withdrawal of an exemption, apply only to those formulas that are manufactured after the compliance date. A postponement of the compliance date may be granted for good cause.

(3) FDA may decide that withdrawal of an exemption is necessary when, on the basis of its review under paragraph (d)(1) of this section, it concludes that quality control procedures are not adequate to ensure that the formula contains all required nutrients, that deviations in nutrient levels are not supported by generally accepted scientific, nutritional, or medical rationale, or that deviations from subpart B of this part are not necessary to provide appropriate directions for preparation and use of the infant formula, or that additional labeling information is necessary.

(4) FDA will use the following criteria in determining whether deviations from the requirements of this subpart are necessary and will adequately protect the public health:

(i) A deviation from the nutrient requirements of section 412(g) of the act or of regulations promulgated under section 412(a)(2) of the act is necessary to provide an infant formula that is appropriate for the dietary management of a specific disease, disorder, or medical condition;

(ii) For exempt infant formulas subject to paragraph (b) of this section, a deviation from the quality control procedures requirements of part 106 is necessary because of unusal or difficult technological problems in manufacturing the infant formula; and

(iii) A deviation from the labeling requirements of subpart B of this part is necessary because label information, including pictograms and symbols required by those regulations, could lead to inappropriate use of the product.

(e) *Notification requirements.* (1) Information required by paragraphs (b) and (c) of this section shall be submitted to Center for Food Safety and Applied Nutrition (HFS–830), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740.

(2) The manufacturer shall promptly notify FDA when the manufacturer has knowledge (as defined in section 412(c)(2) of the act) that reasonably supports the conclusion that an exempt infant formula that has been processed by the manufacturer and that has left an establishment subject to the control of the manufacturer may not provide the nutrients required by paragraph (b) or (c) of this section, or when there is an exempt infant formula that may be otherwise adulterated or misbranded and if so adulterated or misbranded presents a risk of human health. This notification shall be made, by telephone, to the Director of the appropriate FDA district office specified in part 5, subpart M of this chapter. After normal business hours (8 a.m. to 4:30 p.m.), the FDA emergency number, 301–443–1240, shall be used. The manufacturer shall send a followup written confirmation to the Center for Food Safety and Applied Nutrition (HFS–605), Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740, and to the appropriate FDA district office specified in part 5, subpart M of this chapter.

[50 FR 48187, Nov. 22, 1985, as amended at 61 FR 14479, Apr. 2, 1996; 66 FR 17358, Mar. 30, 2001; 66 FR 56035, Nov. 6, 2001; 67 FR 9585, Mar. 4, 2002; 69 FR 17291, Apr. 2, 2004]

Subpart D—Nutrient Requirements

§ 107.100 Nutrient specifications.

(a) An infant formula shall contain the following nutrients at a level not less than the minimum level specified and not more than the maximum level specified for each 100 kilocalories of the infant formula in the form prepared for consumption as directed on the container:

Nutrients	Unit of measurement	Minimum level	Maximum level
Protein	Grams	1.8	4.5
Fat	do	3.3	6.0
	Percent calories	30	54
Linoleic acid	Milligrams	300	.....
	Percent calories	2.7	.....
Vitamins			
Vitamin A	International Units	250	750

Nutrients	Unit of measurement	Minimum level	Maximum level
Vitamin D	do	40	100
Vitamin E	do	0.7	.....
Vitamin K	Micrograms	4	.....
Thiamine (vitamin B_1)	do	40	.....
Riboflavin (vitamin B_2)	do	60	.....
Vitamin B_6	do	35	.....
Vitamin B_{12}	do	0.15	.....
Niacin [1]	do	250	.....
Folic acid (folacin)	do	4	.....
Pantothenic acid	do	300	.....
Biotin [2]	do	1.5	.....
Vitamin C (ascorbic acid)	Milligrams	8	.....
Choline [2]	do	7	.....
Inositol [2]	do	4	.....
Minerals			
Calcium	do	60	.....
Phosphorus	do	30	.....
Magnesium	do	6	.....
Iron	do	0.15	3.0
Zinc	do	0.5	.....
Manganese	Micrograms	5	.....
Copper	Micrograms	60	.....
Iodine	do	5	75
Sodium	Milligrams	20	60
Potassium	do	80	200
Chloride	do	55	150

[1] The generic term "niacin" includes niacin (nicotinic acid) and niacinamide (nicotinamide).
[2] Required only for non-milk-based infant formulas.

In addition to the specifications established in the table in this paragraph for vitamins and minerals, the following also apply:

(b) Vitamin E shall be present at a level of at least 0.7 International Unit of vitamin E per gram of linoleic acid.

(c) Any vitamin K added shall be in the form of phylloquinone.

(d) Vitamin B_6 shall be present at a level of at least 15 micrograms of vitamin B_6 for each gram of protein in excess of 1.8 grams of protein per 100 kilocalories of infant formula in the form prepared for consumption as directed on the container.

(e) The ratio of calcium to phosphorus in infant formula in the form prepared for consumption as directed on the container shall be no less than 1.1 and not more than 2.0.

(f) Protein shall be present in an amount not to exceed 4.5 grams per 100 kilocalories regardless of quality, and not less than 1.8 grams per 100 kilocalories of infant formula in the form prepared for consumption as directed on the container when its biological quality is equivalent to or better than that of casein. If the biological quality of the protein is less than that of casein, the minimum amount of protein shall be increased proportionately to compensate for its lower biological quality. For example, an infant formula containing protein with a biological quality of 75 percent of casein shall contain at least 2.4 grams of protein (1.8/0.75). No protein with a biological quality less than 70 percent of casein shall be used.

[50 FR 45108, Oct. 30, 1985]

Subpart E—Infant Formula Recalls

SOURCE: 54 FR 4008, Jan. 27, 1989, unless otherwise noted.

§ 107.200 Food and Drug Administration-required recall.

When the Food and Drug Administration determines that an adulterated or misbranded infant formula presents a risk to human health, a manufacturer shall immediately take all actions necessary to recall that formula, extending to and including the retail level, consistent with the requirements of this subpart.

§ 107.210 Firm-initiated product removals.

(a) If a manufacturer has determined to recall voluntarily from the market an infant formula that is not subject to § 107.200 but that otherwise violates the laws and regulations administered by the Food and Drug Administration (FDA) and that would be subject to legal action, the manufacturer, upon prompt notification to FDA, shall administer such voluntary recall consistent with the requirements of this subpart.

(b) If a manufacturer has determined to withdraw voluntarily from the market an infant formula that is adulterated or misbranded in only a minor way and that would not be subject to legal action, such removal from the market is deemed to be a market withdrawal, as defined in § 7.3(j) of this chapter. As required by § 107.240(a), the manufacturer shall promptly notify FDA of such violative formula and may, but is not required to, conduct such market withdrawal consistent with the requirements of this subpart pertaining to product recalls.

STANDARD FOR INFANT FORMULA AND FORMULAS FOR SPECIAL MEDICAL PURPOSES INTENDED FOR INFANTS

CODEX STAN 72 – 1981

SECTION A: REVISED STANDARD FOR INFANT FORMULA

PREAMBLE

This standard is divided into two sections. Section A refers to Infant Formula, and Section B deals with Formulas for Special Medical Purposes Intended for Infants.

1. SCOPE

1.1 This section of the Standard applies to infant formula in liquid or powdered form intended for use, where necessary, as a substitute for human milk in meeting the normal nutritional requirements of infants.

1.2 This section of the Standard contains compositional, quality and safety requirements for Infant Formula.

1.3 Only products that comply with the criteria laid down in the provisions of this section of this Standard would be accepted for marketing as infant formula. No product other than infant formula may be marketed or otherwise represented as suitable for satisfying by itself the nutritional requirements of normal healthy infants during the first months of life.

1.4 The application of this section of the Standard should take into account the recommendations made in the International Code of Marketing of Breast-milk Substitutes (1981), the Global Strategy for Infant and Young Child Feeding and World Health Assembly resolution WHA54.2 (2001).

2. DESCRIPTION

2.1 Product Definition

2.1.1 Infant formula means a breast-milk substitute specially manufactured to satisfy, by itself, the nutritional requirements of infants during the first months of life up to the introduction of appropriate complementary feeding.

2.1.2 The product is so processed by physical means only and so packaged as to prevent spoilage and contamination under all normal conditions of handling, storage and distribution in the country where the product is sold.

2.2 Other Definitions

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

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS

3.1 Essential Composition

3.1.1 Infant formula is a product based on milk of cows or other animals or a mixture thereof and/or other ingredients which have been proven to be suitable for infant feeding. The nutritional safety and adequacy of infant formula shall be scientifically demonstrated to support growth and development of infants. All ingredients and food additives shall be gluten-free.

3.1.2 Infant formula prepared ready for consumption in accordance with instructions of the manufacturer shall contain per 100 ml not less than 60 kcal (250 kJ) and not more than 70 kcal (295 kJ) of energy.

3.1.3 Infant formula prepared ready for consumption shall contain per 100 kcal (100 kJ) the following nutrients with the following minimum and maximum or guidance upper levels (GUL)[1], as appropriate. The general principles for establishing these levels are identified in Annex II of this standard.

a) Protein[2), 3), 4)]

Unit	Minimum	Maximum	GUL
g/100 kcal	1.8 [5), 6)]	3.0	-
g/100 kJ	0.45 [5), 6)]	0.7	-

[2)] For the purpose of this standard, the calculation of the protein content of the final product prepared ready for consumption should be based on N x 6.25, unless a scientific justification is provided for the use of a different conversion factor for a particular product. The protein levels set in this standard are based on a nitrogen conversion factor of 6.25. The value of 6.38 is generally established as a specific factor appropriate for conversion of nitrogen to protein in other milk products, and the value of 5.71 as a specific factor for conversion of nitrogen to protein in other soy products.

[3)] For an equal energy value the formula must contain an available quantity of each essential and semi-essential amino acid at least equal to that contained in the reference protein (breast-milk as defined in Annex I); nevertheless for calculation purposes, the concentrations of tyrosine and phenylalanine may be added together. The concentrations of methionine and cysteine may be added together if the ratio is less than 2:1; in the case that the ratio is between 2:1 and 3:1 the suitability of the formula has to be demonstrated by clinical testing.

[4)] Isolated amino acids may be added to Infant Formula only to improve its nutritional value for infants. Essential and semi-essential amino acids may be added to improve protein quality, only in amounts necessary for that purpose. Only L-forms of amino acids shall be used.

[5)] The minimum value applies to cows' milk protein. For infant formula based on non-cows' milk protein other minimum values may need to be applied. For infant formula based on soy protein isolate, a minimum value of 2.25 g/100 kcal (0.5 g/100 kJ) applies.

[6)] Infant formula based on non-hydrolysed milk protein containing less than 2 g protein/ 100 kcal and infant formula based on hydrolysed protein containing less than 2.25 g protein/ 100 kcal should be clinically evaluated.

b) Lipids

Total fat [7, 8)]

Unit	Minimum	Maximum	GUL
g/100 kcal	4.4	6.0	-
g/100 kJ	1.05	1.4	-

[7)] Commercially hydrogenated oils and fats shall not be used in infant formula.

[8)] Lauric and myristic acids are constituents of fats, but combined shall not exceed 20% of total fatty acids. The content of trans fatty acids shall not exceed 3 % of total fatty acids. Trans fatty acids are endogenous components of milk fat. The acceptance of up to 3% of trans fatty acids is intended to allow for the use of milk fat in infant formulae. The erucic acid content shall not exceed 1% of total fatty acids. The total content of phospholipids should not exceed 300 mg/100 kcal (72 mg/100 kJ).

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[1] Guidance upper levels are for nutrients without sufficient information for a science-based risk assessment. These levels are values derived on the basis of meeting nutritional requirements of infants and an established history of apparent safe use. They may be adjusted based on relevant scientific or technological progress. The purpose of the GULs is to provide guidance to manufacturers and they should not be interpreted as goal values. Nutrient contents in infant formulas should usually not exceed the GULs unless higher nutrient levels cannot be avoided due to high or variable contents in constituents of infant formulas or due to technological reasons. When a product type or form has ordinarily contained lower levels than the GULs, manufacturers should not increase levels of nutrients to approach the GULs.

Linoleic acid

Unit	Minimum	Maximum	GUL
mg/100 kcal	300	-	1400
mg/100 kJ	70	-	330

α-Linolenic acid

Unit	Minimum	Maximum	GUL
mg/100 kcal	50	N.S.*	-
mg/100 kJ	12	N.S.	-

*N.S. = not specified

Ratio linoleic/ α-linolenic acid

Min	Max
5:1	15:1

c) Carbohydrates

Total carbohydrates[9)]

Unit	Minimum	Maximum	GUL
g/100 kcal	9.0	14.0	-
g/100 kJ	2.2	3.3	-

[9)] Lactose and glucose polymers should be the preferred carbohydrates in formula based on cows' milk protein and hydrolysed protein. Only precooked and/or gelatinised starches gluten-free by nature may be added to Infant Formula up to 30% of total carbohydrates and up to 2 g/100 ml.

Sucrose, unless needed, and the addition of fructose as an ingredient should be avoided in infant formula, because of potential life-threatening symptoms in young infants with unrecognised hereditary fructose intolerance.

d) Vitamins

Vitamin A

Unit	Minimum	Maximum	GUL
µg RE[10)]/100 kcal	60	180	-
µg RE[10)]/100 kJ	14	43	-

[10)] expressed as retinol equivalents (RE).

1 µg RE = 3.33 IU Vitamin A = 1 µg all-trans retinol. Retinol contents shall be provided by preformed retinol, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

Vitamin D_3

Unit	Minimum	Maximum	GUL
µg[11)]/100 kcal	1	2.5	-
µg[11)]/100 kJ	0.25	0.6	-

[11)] Calciferol. 1 µg calciferol = 40 IU vitamin D

Vitamin E

Unit	Minimum	Maximum	GUL
mg α-TE[12)]/100 kcal	0.5[13)]	-	5
mg α-TE[12)]/100 kJ	0.12[13)]	-	1.2

[12)] 1 mg α-TE (alpha-tocopherol equivalent) = 1 mg d-α-tocopherol

[13)] Vitamin E content shall be at least 0.5 mg α-TE per g PUFA, using the following factors of equivalence to adapt the minimal vitamin E content to the number of fatty acid double bonds in the formula: 0.5 mg -TE/g linoleic acid (18:2 n-6); 0.75 α-TE/g α-linolenic acid (18:3 n-3); 1.0 mg α-TE/g arachidonic acid (20:4 n-6); 1.25 mg α-TE/g eicosapentaenoic acid (20:5 n-3); 1.5 mg α-TE/g docosahexaenoic acid (22:6 n-3).

Vitamin K

Unit	Minimum	Maximum	GUL
µg/100 kcal	4	-	27
µg/100 kJ	1	-	6.5

Thiamin

Unit	Minimum	Maximum	GUL
µg/100 kcal	60	-	300
µg/100 kJ	14	-	72

Riboflavin

Unit	Minimum	Maximum	GUL
µg/100 kcal	80	-	500
µg/100 kJ	19	-	119

Niacin[14)]

Unit	Minimum	Maximum	GUL
µg/100 kcal	300	-	1500
µg/100 kJ	70	-	360

[14)] Niacin refers to preformed niacin.

Vitamin B_6

Unit	Minimum	Maximum	GUL
µg/100 kcal	35	-	175
µg/100 kJ	8.5	-	45

Vitamin B_{12}

Unit	Minimum	Maximum	GUL
µg/100 kcal	0.1	-	1.5
µg/100 kJ	0.025	-	0.36

Pantothenic acid

Unit	Minimum	Maximum	GUL
µg/100 kcal	400	-	2000
µg/100 kJ	96	-	478

Folic acid

Unit	Minimum	Maximum	GUL
µg/100 kcal	10	-	50
µg/100 kJ	2.5	-	12

Vitamin C[15)]

Unit	Minimum	Maximum	GUL
mg/100 kcal	10	-	70[16)]
mg/100 kJ	2.5	-	17[16)]

[15)] expressed as ascorbic acid

[16)] This GUL has been set to account for possible high losses over shelf-life in liquid formulas; for powdered products lower upper levels should be aimed for.

Biotin

Unit	Minimum	Maximum	GUL
µg/100 kcal	1.5	-	10
µg/100 kJ	0.4	-	2.4

e) Minerals and Trace Elements

Iron

Unit	Minimum	Maximum	GUL[17)]
mg/100 kcal	0.45	-	-
mg/100 kJ	0.1	-	-

[17)]Levels may need to be determined by national authorities.

Calcium

Unit	Minimum	Maximum	GUL
mg/100 kcal	50	-	140
mg/100 kJ	12	-	35

Phosphorus

Unit	Minimum	Maximum	GUL
mg/100 kcal	25	-	100[18)]
mg/100 kJ	6	-	24[18)]

[18)] This GUL should accommodate higher needs with soy formula.

Ratio calcium/ phosphorus

Min	Max
1:1	2:1

Magnesium

Unit	Minimum	Maximum	GUL
mg/100 kcal	5	-	15
mg/100 kJ	1.2	-	3.6

Sodium

Unit	Minimum	Maximum	GUL
mg/100 kcal	20	60	-
mg/100 kJ	5	14	-

Chloride

Unit	Minimum	Maximum	GUL
mg/100 kcal	50	160	-
mg/100 kJ	12	38	-

Potassium

Unit	Minimum	Maximum	GUL
mg/100 kcal	60	180	-
mg/100 kJ	14	43	-

Manganese

Unit	Minimum	Maximum	GUL
µg/100 kcal	1	-	100
µg/100 kJ	0.25	-	24

Iodine

Unit	Minimum	Maximum	GUL
µg/100 kcal	10	-	60
µg/100 kJ	2.5	-	14

Selenium

Unit	Minimum	Maximum	GUL
µg/100 kcal	1	-	9
µg/100 kJ	0.24	-	2.2

Copper [19)]

Unit	Minimum	Maximum	GUL
µg/100 kcal	35	-	120
µg/100 kJ	8.5	-	29

[19)] Adjustment may be needed in these levels for infant formula made in regions with a high content of copper in the water supply.

Zinc

Unit	Minimum	Maximum	GUL
mg/100 kcal	0.5	-	1.5
mg/100 kJ	0.12	-	0.36

f) Other Substances

Choline

Unit	Minimum	Maximum	GUL
mg/100 kcal	7	-	50
mg/100 kJ	1.7	-	12

Myo-Inositol

Unit	Minimum	Maximum	GUL
mg/100 kcal	4	-	40
mg/100 kJ	1	-	9.5

L-Carnitine

Unit	Minimum	Maximum	GUL
mg/100 kcal	1.2	N.S.	-
mg/100 kJ	0.3	N.S.	-

3.2 Optional ingredients

3.2.1 In addition to the compositional requirements listed under 3.1.3, other ingredients may be added in order to provide substances ordinarily found in human milk and to ensure that the formulation is suitable as the sole source of nutrition for the infant or to provide other benefits that are similar to outcomes of populations of breastfed babies.

3.2.2 The suitability for the particular nutritional uses of infants and the safety of these substances shall be scientifically demonstrated. The formula shall contain sufficient amounts of these substances to achieve the intended effect, taking into account levels in human milk.

3.2.3 The following substances may be added in conformity with national legislation, in which case their content per 100 kcal (100 kJ) in the Infant Formula ready for consumption shall not exceed:

Taurine

Unit	Minimum	Maximum	GUL
mg/100 kcal	-	12	-
mg/100 kJ	-	3	-

Total nucleotides

Levels may need to be determined by national authorities.

Docosahexaenoic Acid [20)]

Unit	Minimum	Maximum	GUL
% of fatty acids	-	-	0.5

[20)] If docosahexaenoic acid (22:6 n-3) is added to infant formula, arachidonic acid (20:4 n-6) contents should reach at least the same concentration as DHA. The content of eicosapentaenoic acid (20:5 n-3), which can occur in sources of LC-PUFA, should not exceed the content of docosahexaenoic acid. National authorities may deviate from the above conditions, as appropriate for the nutritional needs.

3.2.4 Only L(+)lactic acid producing cultures may be used.

3.3 Fluoride

Fluoride should not be added to infant formula. In any case its level should not exceed 100 µg /100 kcal (24µg/100 kJ) in infant formula prepared ready for consumption as recommended by the manufacturer.

3.4 Vitamin Compounds and Mineral Salts

Vitamins and minerals added in accordance with Section 3.1.3 (d and e) and other nutrients added in accordance with 3.2.1 should be selected from the Advisory Lists of Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children (CAC/GL 10-1979).

3.5 Consistency and Particle Size

When prepared according to the label directions for use, the product shall be free of lumps and of large coarse particles and suitable for adequate feeding of young infants.

3.6 Purity Requirements

All ingredients shall be clean, of good quality, safe and suitable for ingestion by infants. They shall conform with their normal quality requirements, such as colour, flavour and odour.

3.7 Specific Prohibitions

The product and its component shall not have been treated by ionizing irradiation.

4. FOOD ADDITIVES

Only the food additives listed in this Section or in the Codex Advisory List of Mineral Salts and Vitamin Compounds for Use in Foods for Infants and Children (CAC/GL 10-1979) may be present in the foods described in section 2.1 of this Standard, as a result of carry-over from a raw material or other ingredient (including food additive) used to produce the food, subject to the following conditions:

a) The amount of the food additive in the raw materials or other ingredients (including food additives) does not exceed the maximum level specified; and

b) The food into which the food additive is carried over does not contain the food additive in greater quantity than would be introduced by the use of the raw materials or ingredients under good manufacturing practice, consistent with the provisions on carry-over in the Preamble of the General Standard for Food Additives (CAC/STAN 192-1995).

The following food additives are acceptable for use in the preparation of infant formula, as described in Section 2.1 of this Standard (in 100 ml of product, ready for consumption prepared following manufacturer's instructions, unless otherwise indicated):

INS	Additive	Maximum level in 100 ml of the product ready for consumption
4.1 Thickeners		
412	Guar gum	0.1 g in liquid formulas containing hydrolysed protein
410	Carob bean gum (Locust bean gum)	0.1 g in all types of infant formula
1412	Distarch phosphate	0.5 g singly or in combination in soy-based infant formula only 2.5 g singly or in combination in hydrolyzed protein- and/or amino acid based infant formula only
1414	Acetylated distarch phosphate	
1413	Phosphated distarch phosphate	
1440	Hydroxypropyl starch	
407	Carrageenan[2]	0.03 g in regular milk-and soy-based liquid infant formula only 0.1 g in hydrolysed protein- and/or amino acid based liquid infant formula only
4.2 Emulsifiers		
322	Lecithins	0.5 g in all types of infant formula[22)]
471	Mono- and diglycerides	0.4 g in all types of infant formula[22)]
4.3 Acidity Regulators		
524	Sodium hydroxide	0.2 g singly or in combination and within the limits for sodium, potassium and calcium in section 3.1.3 (e) in all types of infant formula
500ii	Sodium hydrogen carbonate	0.2 g singly or in combination and within the limits for sodium, potassium and calcium in section 3.1.3 (e) in all types of infant formula
500i	Sodium carbonate	
525	Potassium hydroxide	
501ii	Potassium hydrogen carbonate	
501i	Potassium carbonate	
526	Calcium hydroxide	
270	L(+) lactic acid	Limited by GMP in all types of infant formula

[2] Not endorsed by the 39th Session of the CCFA. JECFA evaluation is pending. national authorities may restrict its use until JECFA evaluation has been completed.

[22)] If more than one of the substances INS 322, 471 are added the maximum level for each of those substances is lowered with the relative part as present of the other substances

INS	Additive	Maximum level in 100 ml of the product ready for consumption
330	Citric acid	Limited by GMP in all types of infant formula
331i	Sodium dihydrogen citrate	Limited by GMP in all types of infant formula
331iii	Trisodium citrate	Limited by GMP in all types of infant formula
332	Potassium citrate	Limited by GMP in all types of infant formula
4.4 Antioxidants		
307b	Mixed tocopherol concentrate	1 mg in all types of infant formula singly or in combination
304i	Ascorbyl palmitate	1 mg in all types of infant formula singly or in combination
4.9 Packaging Gases		
290	Carbon dioxide	GMP
941	Nitrogen	

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 not contain contaminants or undesirable substances (e.g. biologically active substances) in amounts which may represent a hazard to the health of the infant. The product covered by the provisions of the Standard shall comply with those maximum residue limits and maximum levels established by the Codex Alimentarius Commission.

	Maximum level
Lead	0.02 mg/kg (in the ready-to-use product)

6. HYGIENE

6.1 It is recommended that the product covered by the provisions of this standard be prepared and handled in accordance with the appropriate sections of the Recommended International Code of Practice - General Principles of Food Hygiene (CAC/RCP 1-1969), and other relevant Codex texts such as the Recommended International Code of Hygienic Practice for Foods for Infants and Children (CAC/RCP 21-1979).

6.2 The products should comply with any microbiological criteria established in accordance with the Principles for the Establishment and Application of Microbiological Criteria for Foods (CAC/GL 21-1997).

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 CONTAINER

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

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

(ii) not less than 85% v/v for products in the weight range 150-250 g (5-8 oz.); and

(iii) not less than 90% v/v for products weighing more than 250 g (8 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 completely filled.

9. LABELLING

The requirements of the Codex General Standard for the Labelling of Prepackaged Foods (CODEX STAN 1-1985), the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985) and the Guidelines for Use of Nutrition and Health Claims apply to infant formula and formula for special medical purposes for infants. These requirements include a prohibition on the use of nutrition and health claims for foods for infants and young children except where specifically provided for in relevant Codex Standards or national legislation. In addition to these requirements the following specific provisions apply:

9.1 The Name of the Food

9.1.1 The text of the label and all other information accompanying the product shall be written in the appropriate language(s).

9.1.2 The name of the product shall be either "Infant Formula" or any appropriate designation indicating the true nature of the product, in accordance with national usage.

9.1.3 The sources of protein in the product shall be clearly shown on the label.

9.1.4 If cows' milk is the only source of protein, the product may be labelled "Infant Formula Based on Cows' Milk".

9.1.5 A product which contains neither milk or any milk derivative shall be labelled "contains no milk or milk products" or an equivalent phrase.

9.2 List of Ingredients

9.2.1 A complete list of ingredients shall be declared on the label in descending order of proportion except that in the case of added vitamins and minerals, these ingredients may be arranged as separate groups for vitamins and minerals. Within these groups the vitamins and minerals need not be listed in descending order of proportion.

9.2.2 The specific name shall be declared for ingredients of animal or plant origin and for food additives. In addition, appropriate class names for these ingredients and additives may be included on the label.

9.3 Declaration of Nutritive Value

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

a) the amount of energy, expressed in kilocalories (kcal) and/or kilojoules (kJ), and the number of grammes of protein, carbohydrate and fat per 100 grammes or per 100 milliliters of the food as sold as well as per 100 milliliters of the food ready for use, when prepared according to the instructions on the label.

b) the total quantity of each vitamin, mineral, choline as listed in paragraph 3.1.3 and any other ingredient as listed in paragraph 3.2 of this Standard per 100 grammes or per 100 milliliters of the food as sold as well as per 100 milliliters of the food ready for use, when prepared according to the instructions on the label.

c) In addition, the declaration of nutrients in a) and b) per 100 kilocalories (or per 100 kilojoules) is permitted.

9.4 Date Marking and Storage Instructions

9.4.1 The date of minimum durability (preceded by the words "best before") shall be declared by the day, month and year in uncoded numerical sequence except that for products with a shelf-life of more than three months, the month and year will suffice. The month may be indicated by letters in those countries where such use will not confuse the consumer.

In the case of products requiring a declaration of month and year only, and the shelf-life of the product is valid to the end of a given year, the expression "end (stated year)" may be used as an alternative.

9.4.2 In addition to the date, any special conditions for the storage of the food shall be indicated if the validity of the date depends thereon.

Where practicable, storage instructions shall be in close proximity to the date marking.

9.5 Information for Use

9.5.1 Products in liquid form may be used either directly or in the case of concentrated liquid products, must be prepared with water that is safe or has been rendered safe by previous boiling before feeding, according to directions for use. Products in powder form should be reconstituted with water that is safe or has been rendered safe by previous boiling for preparation. Adequate directions for the appropriate preparation and handling should be in accordance with Good Hygienic Practice.

9.5.2 Adequate directions for the appropriate preparations and use of the product, including its storage and disposal after preparation, i.e. that formula remaining after feeding should be discarded, shall appear on the label and in any accompanying leaflet.

9.5.3 The label shall carry clear graphic instructions illustrating the method of preparation of the product.

9.5.4 The directions should be accompanied by a warning about the health hazards of inappropriate preparation, storage and use.

9.5.5 Adequate directions regarding the storage of the product after the container has been opened, shall appear on the label and in any accompanying leaflet.

9.6 Additional Labelling Requirements

9.6.1 Labels should not discourage breastfeeding. Each container label shall have a clear, conspicuous and easily readable message which includes the following points:

a) the words "important notice" or their equivalent;

b) the statement "Breast milk is the best food for your baby" or a similar statement as to the superiority of breastfeeding or breast milk;

c) a statement that the product should only be used on advice of a independent health worker as to the need for its use and the proper method of use.

9.6.2 The label shall have no pictures of infants and women nor any other picture or text which idealizes the use of infant formula.

9.6.3 The terms "humanized", "maternalized" or other similar terms shall not be used.

9.6.4 Information shall appear on the label to the effect that infants should receive complementary foods in addition to the formula, from an age that is appropriate for their specific growth and development needs, as advised by an independent health worker, and in any case from the age over six months.

9.6.5 The products shall be labelled in such a way as to avoid any risk of confusion between infant formula, follow-up formula, and formula for special medical purposes.

10. METHODS OF ANALYSIS AND SAMPLING[3]

[3] To be finalized.

Annex I

Essential and semi-essential amino acids in breast milk*

For the purpose of this Standard the essential and semi-essential amino acids in human milk from published studies which report measurements of the total nitrogen content and/or the calculation method of the protein content, expressed as mg per g of nitrogen and as mg per 100 kcal are listed.

The average level of an amino acid (mg per g of nitrogen) from each study was used to calculate the corresponding amino acid content per 100 kcal of an infant formula with the minimum protein content of 1.8 g/ 100 kcal accepted in this Standard (mg amino acid/g nitrogen in breast-milk divided by the nitrogen conversion factor of 6.25 and multiplied by 1.8).

The mean of the sums of the average amino acid levels from all studies was converted in the same manner to the average amounts of an amino acid per g of protein (total nitrogen x 6.25) and per 100 kcal of energy (columns 19 and 20 of the table).

National authorities may use all of the listed values.

** Adapted from Koletzko B, Baker S, Cleghorn G, et al, Global standard for the composition of infant formula: Recommendations of ESPGHAN coordinated international expert group. J Pediatr Gastroenterol Nutr. 2005;41:584-599.*

	Lönnerdal &Forsum (1985)		**Darragh & Moughan (1998)**		**Bindels & Harzer (1985)**		**Janas et al. (1987)**		**Villalpando et al. (1998)**				**Räihä et al. (2002) mod Nayman et al. (1979)**		**Yonekubo et al. (1991)**		**Mean of all amino acids contents**		
	Pooled banked milk at 4-16 weeks		**Pooled over 20 days at 10-14 weeks (n=20)**		**24 hours, pooled at 5 weeks (n=10)**		**24 hours, pooled at 8 weeks (n=10)**		**24 hours, pooled at 4-6 months**				**Pooled banked milk at >1 month**		**Milk at 21 days –2 months**				
									Mexico (n=40)		**Houston (n=40)**								
mg amino acid per	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g nitro-gen**	**g pro-tein**	**100 kcal**
Cysteine	111	*32*	173	*50*	108	*31*	101	*29*	167	*48*	134	*39*	133	*38*	118	*34*	131	21	*38*
Histidine	111	*32*	156	*45*	255	*73*	112	*32*	112	*32*	108	*31*	122	*35*	150	*43*	141	23	*41*

	Lönnerdal &Forsum (1985)		**Darragh & Moughan (1998)**		**Bindels & Harzer (1985)**		**Janas et al. (1987)**		**Villalpando et al. (1998)**				**Räihä et al. (2002) mod Nayman et al. (1979)**		**Yonekubo et al. (1991)**		**Mean of all amino acids contents**		
	Pooled banked milk at 4-16 weeks		**Pooled over 20 days at 10-14 weeks (n=20)**		**24 hours, pooled at 5 weeks (n=10)**		**24 hours, pooled at 8 weeks (n=10)**		**24 hours, pooled at 4-6 months**				**Pooled banked milk at >1 month**		**Milk at 21 days –2 months**				
									Mexico (n=40)		**Houston (n=40)**								
mg amino acid per	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g nitro-gen**	**g pro-tein**	**100 kcal**
Isoleucine	242	70	333	96	376	108	306	88	292	84	331	95	300	86	374	108	319	51	92
Leucine	457	*132*	598	*172*	713	*205*	611	*176*	528	*152*	541	*156*	572	*165*	667	*192*	586	94	*169*
Lysine	314	*90*	406	*117*	522	*150*	365	*105*	366	*105*	408	*118*	361	*104*	421	*121*	395	63	*114*
Methionine	78	*22*	90	*26*	89	*26*	73	*21*	99	*29*	76	*22*	83	*24*	92	*26*	85	14	*24*
Phenyl-alanine	153	*44*	243	*70*	344	*99*	183	*53*	440	*127*	439	*126*	217	*62*	240	*69*	282	45	*81*
Threonine	217	*62*	316	*91*	344	*99*	251	*72*	248	*71*	242	*70*	256	*74*	269	*77*	268	43	*77*
Tryptophan	NA		NA		172	*50*	79	*23*	112	*32*	89	*26*	111	*32*	122	*35*	114	18	*33*
Tyrosine	201	*58*	241	*69*	369	*106*	191	*55*	292	*84*	299	*86*	233	*67*	249	*72*	259	42	*75*

	Lönnerdal &Forsum (1985)		**Darragh & Moughan (1998)**		**Bindels & Harzer (1985)**		**Janas et al. (1987)**		**Villalpando et al. (1998)**				**Räihä et al. (2002) mod Nayman et al. (1979)**		**Yonekubo et al. (1991)**		**Mean of all amino acids contents**		
	Pooled banked milk at 4-16 weeks		**Pooled over 20 days at 10-14 weeks (n=20)**		**24 hours, pooled at 5 weeks (n=10)**		**24 hours, pooled at 8 weeks (n=10)**		**24 hours, pooled at 4-6 months**				**Pooled banked milk at >1 month**		**Milk at 21 days –2 months**				
									Mexico (n=40)		**Houston (n=40)**								
mg amino acid per	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g N**	**100 kcal**	**g nitro-gen**	**g pro-tein**	**100 kcal**
Valine	253	*73*	327	*94*	376	*108*	267	*77*	286	*82*	331	*95*	317	*91*	364	*105*	315	50	*90*

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Annex II

GENERAL PRINCIPLES FOR ESTABLISHING MINIMUM AND MAXIMUM VALUES FOR THE ESSENTIAL COMPOSITION OF INFANT FORMULA

1. The goal of establishing minimum and maximum values is to provide safe and nutritionally adequate infant formula products that meet the normal nutritional requirements of infants.

2. A nutritionally adequate infant formula will promote growth and development consistent with science based standards and meet the nutritional requirements of infants when fed as a sole source of nutrition during the first months of life up to the introduction of appropriate complementary feeding.

3. The values to be established are based on an independent evaluation, in particular of the scientific evidence of the amounts needed to meet the nutritional requirements of infants, considering relevant human infant studies and the composition of breast-milk.

4. In addition to the principles set out in No. 3, when setting minimum and maximum values, consideration will also be given to the safety of such values.

For nutrients with a documented risk of adverse health effects the upper levels to be taken into account will be determined using a science-based risk assessment approach. Where scientific data are not sufficient for a science-based risk assessment, consideration should be given to an established history of apparently safe use of the nutrient in infants, as appropriate. Values derived on the basis of meeting the nutritional requirements of infants and an established history of apparently safe use should be considered as interim guidance upper levels. The approach to setting maximum and upper guidance values shall be made transparent and comprehensible.

5. When establishing minimum and maximum amounts, the following should also be taken into account:

a) bioavailability, processing losses and shelf-life stability from the ingredients and formula matrix,

b) total levels of a nutrient in infant formula, taking into account both naturally occurring nutrients in the ingredients and added nutrients,

c) the inherent variability of nutrients in ingredients and in water that may be added to the infant formula during manufacture.

6. Overages for individual nutrients, as appropriate, to ensure that the required minimum levels are met throughout the shelf-life of the formula, will be included in the maximum value.

7. In establishing minimum or maximum amounts of nutrients per 100 kcal (or per 100 kJ) of infant formula based on consideration of reference values for the nutrients expressed as units per daily intake or per kilogram of body weight, the following assumptions will be considered:

a) The mean intake of prepared formula for infants from birth to six months of age is 750 ml per day, and

b) a representative body weight for an infant over this period is 5 kg,

and

c) a representative caloric intake of an infant over this period is 500 kcal per day (or 100 kcal/kg/day).

Modifications of the approach may be needed when there is justification for deviating from one or more of these assumptions with regard to the specific formula product or specific infant population group.

SECTION B: FORMULA FOR SPECIAL MEDICAL PURPOSES INTENDED FOR INFANTS

1. SCOPE

1.1 This section of the Standard applies to Formula for Special Medical Purposes Intended for Infants in liquid or powdered form intended for use, where necessary, as a substitute for human milk or infant formula in meeting the special nutritional requirements arising from the disorder, disease or medical condition for whose dietary management the product has been formulated.

1.2 This section of the Standard contains compositional, quality, labelling and safety requirements for Formula for Special Medical Purposes Intended for Infants.

1.3 Only products that comply with the criteria laid down in the provisions of this section of this standard would be accepted for marketing as formula for special medical purposes intended for infants.

1.4 The application of this section of the Standard should take into account, as appropriate for the products to which the section applies and the special needs of the infants for whom they are intended, the recommendations made in the International Code of Marketing of Breast-milk Substitutes (1981), the Global Strategy for Infant and Young Child Feeding and World Health Assembly resolution WHA54.2 (2001).

2. DESCRIPTION

2.1 Product definition

2.1.1 Formula for Special Medical Purposes Intended for Infants means a substitute for human milk or infant formula that complies with Section 2, Description, of the Codex Standard for the Labelling of and Claims for Foods for Special Medical Purposes (CODEX STAN 180-1991) and is specially manufactured to satisfy, by itself, the special nutritional requirements of infants with specific disorders, diseases or medical conditions during the first months of life up to the introduction of appropriate complementary feeding.

2.1.2

See Section A 2.1.2

2.2 Other Definitions

See Section A 2.2

3. ESSENTIAL COMPOSITION AND QUALITY FACTORS

3.1 Essential Composition

3.1.1. Formula for Special Medical Purposes intended for Infants is a product based on ingredients based of animal, plant and/or synthetic origin suitable for human consumption. All ingredients and food additives shall be gluten-free.

3.1.2 The composition of Formula for Special Medical Purposes Intended for Infants shall be based on sound medical and nutritional principles. The nutritional safety and adequacy of the formula shall be scientifically demonstrated to support growth and development in the infants for whom it is intended,

as appropriate for the specific products and indications. Their use shall be demonstrated by scientific evidence to be beneficial in the dietary management of the infants for whom it is intended.

3.1.3 The energy content and nutrient composition of Formula for Special Medical Purposes intended for infants shall be based on the requirements for infant formula as given in sections A 3.1.2 and A 3.1.3, except for the compositional provisions which must be modified to meet the special nutritional requirements arising from the disease(s), disorder(s) or medical condition(s) for whose dietary management the product is specifically formulated, labelled and presented.

3.1.4 In addition to the requirements in 3.1.3 the following requirements shall also be taken into account, where appropriate:

Chromium

Unit	**Minimum**	**Maximum**	**GUL**
µg/100 kcal	1.5	-	10
µg/100 kJ	0.4	-	2.4

Molybdenum

Unit	**Minimum**	**Maximum**	**GUL**
µg/100 kcal	1.5	-	10
µg/100 kJ	0.4	-	2.4

3.2 Optional ingredients

3.2.1 In addition to the compositional requirements listed under 3.1.3, other ingredients may be added in order to provide substances ordinarily found in human milk or required to ensure that the formulation is suitable as the sole source of nutrition for the infant and for the dietary management of his/her disease, disorder or medical condition.

3.2.2 The suitability for the intended special medical purpose, the suitability for the particular nutritional use of infants and the safety of these substances shall be scientifically demonstrated. The formula shall contain sufficient amounts of these substances to achieve the intended effect.

3.2.3 Only L(+)lactic acid producing cultures may be used in Formulas for Special Medical Purposes for infants if shown to be safe and appropriate for use in these vulnerable populations.

3.3 Vitamin Compounds and Mineral Salts

See Section A 3.4

3.4 Consistency and Particle Size

See Section A 3.5

3.5 Purity Requirements

See Section A 3.6

3.6 Specific Prohibitions

See Section A 3.7

4. FOOD ADDITIVES

See Section A 4.

5. CONTAMINANTS

See Section A 5.

6. HYGIENE

See Section A 6.

7. PACKAGING

See Section A 7.

8. FILL OF CONTAINER

See Section A 8.

9. LABELLING

See introductory paragraph of Section A 9.

9.1 The Name of the Food

9.1.1 See Section A 9.1.1

9.1.2 The name of the product shall be "Formula for Special Medical Purposes Intended for Infants" or any appropriate designation indicating the true nature of the product, in accordance with national usage.

9.1.3 If cows' milk is the only source of protein, the product may be labelled "Formula for Special Medical Purposes Intended for Infants Based on Cows' Milk".

9.2 List of Ingredients

See Section A 9.2

9.3 Declaration of Nutritive Value

Formula for Special Medical Purposes Intended for Infants shall be labelled with complete nutrition labelling according to Section 4.2 of Codex Standard for the Labelling of and Claims for Foods for Special Medical Purposes (CODEX STAN 180-1991).

9.4 Date Marking and Storage Instructions

See Section A 9.4

9.5 Information for Use

See Section A 9.5

9.6 Additional Labelling Requirements

9.6.1 Formula for Special Medical Purposes Intended for Infants shall be labelled with the additional information as specified in Sections 4.4.1, 4.4.3, 4.4.4, 4.5.1 and 4.5.5 of CODEX STAN 180-1991.

9.6.2 A prominent statement indicating that the product is intended as the sole source of nutrition shall appear on the label.

9.6.3 In addition, the information specified in Sections 4.5.2, 4.5.3 and 4.5.6 of CODEX STAN 180-1991 shall be included on the label or be provided separately from the package.

9.6.4 Labels and information provided separately from the package should not discourage breastfeeding, unless breastfeeding is contraindicated on medical grounds for the disease(s), disorder(s) or medical condition(s) for which the product is intended.

9.6.5

See Section A 9.6.5

10. Methods of Analysis

See Section A 10.

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HALAL

U-D 1 QT (946 mL)

NUTRIENTS PER 100 CALORIES (5 FL OZ)

PROTEIN	2.07	G	WATER	133	G
FAT	5.40	G	LINOLEIC ACID	860	MG
CARBOHYDRATE	10.9	G			

VITAMINS

VITAMIN A	300	IU	NIACIN	1050	MCG
VITAMIN D	60	IU	FOLIC ACID (FOLACIN)	15	MCG
VITAMIN E	1.5	IU	PANTOTHENIC ACID	450	MCG
VITAMIN K	8	MCG	BIOTIN	4.4	MCG
THIAMIN (VIT. B_1)	100	MCG	VITAMIN C (ASCORBIC ACID)	9	MG
RIBOFLAVIN (VIT. B_2)	150	MCG	CHOLINE	16	MG
VITAMIN B_6	60	MCG	INOSITOL	4.7	MG
VITAMIN B_{12}	0.25	MCG			

MINERALS

CALCIUM	78	MG	COPPER	90	MCG
PHOSPHORUS	42	MG	IODINE	6	MCG
MAGNESIUM	6	MG	SELENIUM	1.8	MCG
IRON	1.8	MG	SODIUM	24	MG
ZINC	0.75	MG	POTASSIUM	105	MG
MANGANESE	5	MCG	CHLORIDE	65	MG

INGREDIENTS: WATER, **ORGANIC** NONFAT MILK, **ORGANIC** MALTODEXTRIN, **ORGANIC** SUGAR, **ORGANIC** HIGH OLEIC SUNFLOWER OIL, **ORGANIC** SOY OIL, **ORGANIC** COCONUT OIL; **LESS THAN 0.5% OF:** C. COHNII OIL*, M. ALPINA OIL†, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, CARRAGEENAN, MAGNESIUM CHLORIDE, SALT, FERROUS SULFATE, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, d-ALPHA-TOCOPHERYL ACETATE, L-CARNITINE, ZINC SULFATE, NIACINAMIDE, CALCIUM PANTOTHENATE, RIBOFLAVIN, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, POTASSIUM IODIDE, SODIUM SELENATE, VITAMIN D_3, CYANOCOBALAMIN, POTASSIUM HYDROXIDE AND NUCLEOTIDES (ADENOSINE 5'-MONOPHOSPHATE, CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)

USE AS DIRECTED BY A DOCTOR
Directions for Preparation and Use

USE BY DATE ON BOTTLE • DO NOT ADD WATER
DO NOT USE IF BAND AROUND CAP OR INNER FOIL SEAL IS DAMAGED.

Your baby's health depends on carefully following these directions. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to boil (sterilize) bottles, nipples and rings before use.

Use

Shake very well before each use

Remove protective band; twist off and clean cap

Invert cap; press down to pierce foil, then turn cap a half turn

Remove foil

Pour formula into bottle; attach nipple

Once feeding begins, use within 1 hour or discard

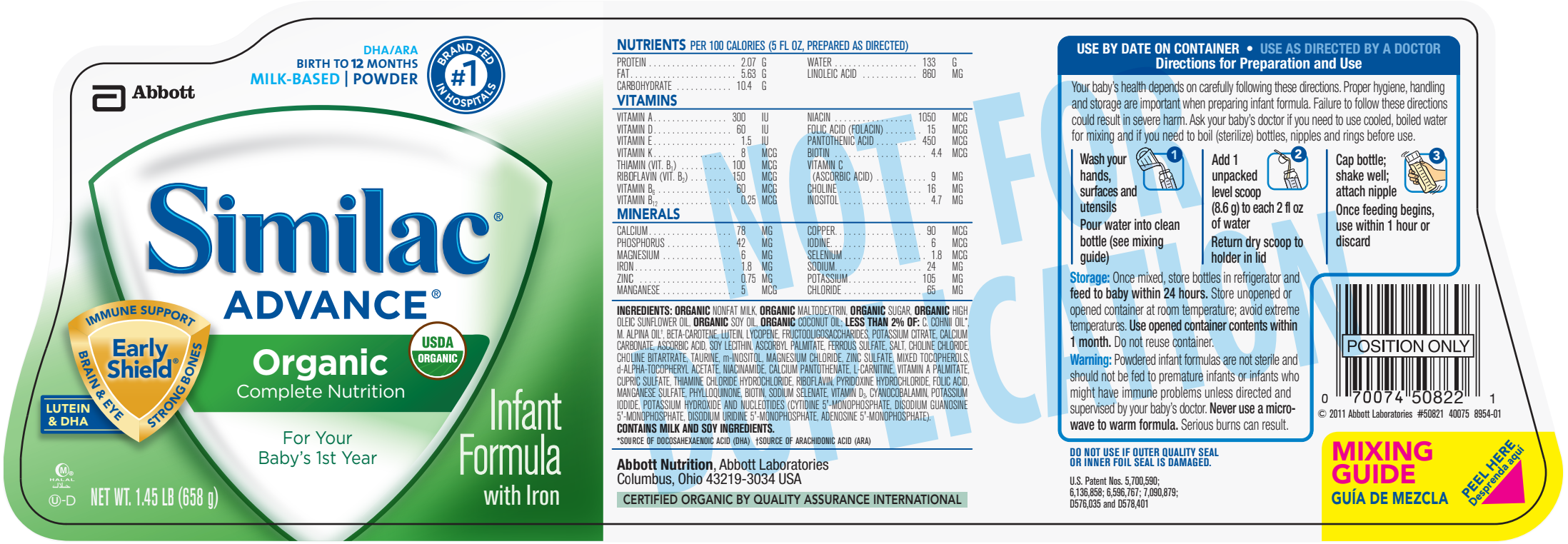
Prepare and feed all formula in this container within 3 days after opening.

Storage Once opened, store quart bottle in refrigerator. Store prepared bottles in refrigerator and **feed to baby within 48 hours.** Store unopened containers at room temperature; avoid extreme temperatures. Do not reuse container.

Warning Do not use this container to warm formula. **Never use a microwave to warm formula.** Serious burns can result.

Abbott Nutrition, Abbott Laboratories, Columbus, Ohio 43219-3034 USA

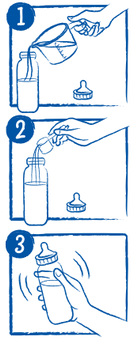
CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL


DHA/ARA
BIRTH TO 12 MONTHS
MILK-BASED | POWDER
BRAND FED #1 IN HOSPITALS
Abbott
Similac®
ADVANCE®
IMMUNE SUPPORT
Early Shield®
BRAIN & EYE
STRONG BONES
LUTEIN & DHA
USDA ORGANIC
Organic
Complete Nutrition
For Your Baby's 1st Year
Infant Formula with Iron
NET WT. 1.45 LB (658 g)
U-D
NUTRIENTS PER 100 CALORIES (5 FL OZ, PREPARED AS DIRECTED)
PROTEIN 2.07 G
FAT 5.63 G
CARBOHYDRATE 10.4 G
WATER 133 G
LINOLEIC ACID 860 MG
VITAMINS
VITAMIN A 300 IU
VITAMIN D 60 IU
VITAMIN E 1.5 IU
VITAMIN K 8 MCG
THIAMIN (VIT. B1) 100 MCG
RIBOFLAVIN (VIT. B2) 150 MCG
VITAMIN B6 60 MCG
VITAMIN B12 0.25 MCG
NIACIN 1050 MCG
FOLIC ACID (FOLACIN) 15 MCG
PANTOTHENIC ACID 450 MCG
BIOTIN 4.4 MCG
VITAMIN C (ASCORBIC ACID) 9 MG
CHOLINE 16 MG
INOSITOL 4.7 MG
MINERALS
CALCIUM 78 MG
PHOSPHORUS 42 MG
MAGNESIUM 6 MG
IRON 1.8 MG
ZINC 0.75 MG
MANGANESE 5 MCG
COPPER 90 MCG
IODINE 6 MCG
SELENIUM 1.8 MCG
SODIUM 24 MG
POTASSIUM 105 MG
CHLORIDE 55 MG
INGREDIENTS: ORGANIC NONFAT MILK, ORGANIC MALTODEXTRIN, ORGANIC SUGAR, ORGANIC HIGH OLEIC SUNFLOWER OIL, ORGANIC SOY OIL, ORGANIC COCONUT OIL; LESS THAN 2% OF: C. COHNII OIL*, M. ALPINA OIL†, BETA-CAROTENE, LUTEIN, LYCOPENE, FRUCTOOLIGOSACCHARIDES, POTASSIUM CITRATE, CALCIUM CARBONATE, ASCORBIC ACID, SOY LECITHIN, ASCORBYL PALMITATE, FERROUS SULFATE, SALT, CHOLINE CHLORIDE, CHOLINE BITARTRATE, TAURINE, m-INOSITOL, MAGNESIUM CHLORIDE, ZINC SULFATE, MIXED TOCOPHEROLS, d-ALPHA-TOCOPHERYL ACETATE, NIACINAMIDE, CALCIUM PANTOTHENATE, L-CARNITINE, VITAMIN A PALMITATE, CUPRIC SULFATE, THIAMINE CHLORIDE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, FOLIC ACID, MANGANESE SULFATE, PHYLLOQUINONE, BIOTIN, SODIUM SELENATE, VITAMIN D3, CYANOCOBALAMIN, POTASSIUM IODIDE, POTASSIUM HYDROXIDE AND NUCLEOTIDES (CYTIDINE 5'-MONOPHOSPHATE, DISODIUM GUANOSINE 5'-MONOPHOSPHATE, DISODIUM URIDINE 5'-MONOPHOSPHATE, ADENOSINE 5'-MONOPHOSPHATE).
CONTAINS MILK AND SOY INGREDIENTS.
*SOURCE OF DOCOSAHEXAENOIC ACID (DHA) †SOURCE OF ARACHIDONIC ACID (ARA)
Abbott Nutrition, Abbott Laboratories
Columbus, Ohio 43219-3034 USA
CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL
USE BY DATE ON CONTAINER • USE AS DIRECTED BY A DOCTOR
Directions for Preparation and Use
Your baby's health depends on carefully following these directions. Proper hygiene, handling and storage are important when preparing infant formula. Failure to follow these directions could result in severe harm. Ask your baby's doctor if you need to use cooled, boiled water for mixing and if you need to boil (sterilize) bottles, nipples and rings before use.
1 Wash your hands, surfaces and utensils
Pour water into clean bottle (see mixing guide)
2 Add 1 unpacked level scoop (8.6 g) to each 2 fl oz of water
Return dry scoop to holder in lid
3 Cap bottle; shake well; attach nipple
Once feeding begins, use within 1 hour or discard
Storage: Once mixed, store bottles in refrigerator and feed to baby within 24 hours. Store unopened or opened container at room temperature; avoid extreme temperatures. Use opened container contents within 1 month. Do not reuse container.
Warning: Powdered infant formulas are not sterile and should not be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor. Never use a microwave to warm formula. Serious burns can result.
DO NOT USE IF OUTER QUALITY SEAL OR INNER FOIL SEAL IS DAMAGED.
U.S. Patent Nos. 5,700,590; 6,136,858; 6,596,767; 7,090,879; D576,035 and D578,401
POSITION ONLY
0 70074 50822 1
© 2011 Abbott Laboratories #50821 40075 8954-01
MIXING GUIDE
GUÍA DE MEZCLA
PEEL HERE
Despréndala aquí

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. If you choose to supplement breastfeeding with formula or to formula feed exclusively, there is no better formula than Vermont Organics™ ORGANIC Infant Formula DHA and ARA. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**



1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.7 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.4 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.1 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (34.8 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (123 g)

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.

Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.

Filled by weight, not by volume. Contents may settle during shipment.

Contents yield approximately 190 fl oz of formula

Las instrucciones en Español se encuentran al dorso de esta etiqueta.

Easy to Digest
Powder • Add Water

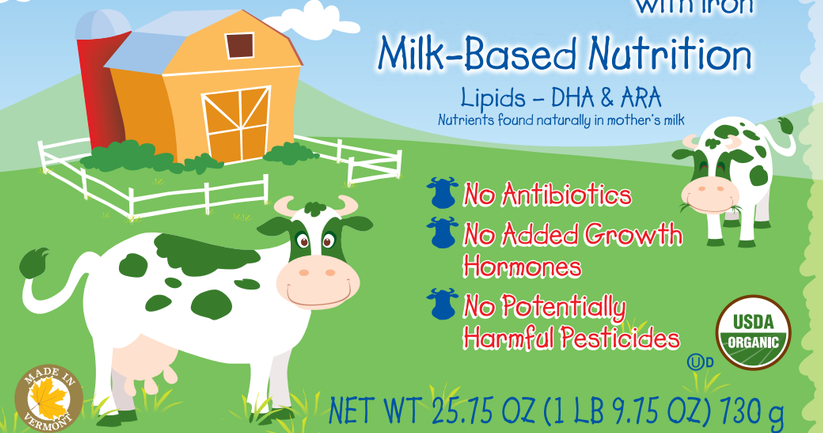
Vermont Organics™

For Babies
0-12 Months

organic infant formula with iron

Milk-Based Nutrition

Lipids – DHA & ARA
Nutrients found naturally in mother's milk



- No Antibiotics
- No Added Growth Hormones
- No Potentially Harmful Pesticides

USDA ORGANIC

UD

MADE IN VERMONT

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** REDUCED MINERALS WHEY, **ORGANIC** VEGETABLE OILS (PALM OR PALM OLEIN, HIGH OLEIC (SAFFLOWER OR SUNFLOWER), COCONUT, SOY), **ORGANIC** NONFAT MILK, **ORGANIC** LACTOSE, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, VITAMIN A PALMITATE, BETA-CAROTENE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (dl-ALPHA TOCOPHERYL ACETATE), MIXED TOCOPHEROL CONCENTRATE, VITAMIN K (PHYTONADIONE), ASCORBYL PALMITATE, THIAMINE HYDROCHLORIDE, RIBOFLAVIN, PYRIDOXINE HYDROCHLORIDE, CYANOCOBALAMIN, NIACINAMIDE, FOLIC ACID, CALCIUM PANTOTHENATE, BIOTIN, ASCORBIC ACID, CHOLINE CHLORIDE, INOSITOL, CALCIUM CHLORIDE, CALCIUM HYDROXIDE, FERROUS SULFATE, ZINC SULFATE, MANGANESE SULFATE, CUPRIC SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM IODIDE, POTASSIUM HYDROXIDE, SODIUM SELENITE, SODIUM CITRATE, TAURINE, SOY LECITHIN, NUCLEOTIDES (ADENOSINE-5'-MONOPHOSPHATE, CYTIDINE-5'-MONOPHOSPHATE, DISODIUM GUANOSINE-5'- MONOPHOSPHATE, DISODIUM INOSINE-5'-MONOPHOSPHATE, DISODIUM URIDINE-5'MONOPHOSPHATE).

CONTAINS MILK AND SOY INGREDIENTS.

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g	2.2
FAT g	5.3
CARBOHYDRATE g	10.6
WATER g	134
LINOLEIC ACID mg	750
VITAMINS:	
VITAMIN A IU	300
VITAMIN D IU	60
VITAMIN E IU	2
VITAMIN K mcg	8
THIAMINE (VITAMIN B_1) mcg	100
RIBOFLAVIN (VITAMIN B_2) mcg	150
VITAMIN B_6 mcg	63
VITAMIN B_{12} mcg	0.2
NIACIN mcg	750
FOLIC ACID (FOLACIN) mcg	7.5
PANTOTHENIC ACID mcg	315

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg	2.3
VITAMIN C (ASCORBIC ACID) mg	9
CHOLINE mg	15
INOSITOL mg	4.1
MINERALS:	
CALCIUM mg	63
PHOSPHORUS mg	42
MAGNESIUM mg	7
IRON mg	1.8
ZINC mg	0.75
MANGANESE mcg	15
COPPER mcg	71
IODINE mcg	9
SELENIUM mcg	2.1
SODIUM mg	23
POTASSIUM mg	84
CHLORIDE mg	56

DISTRIBUTED BY:
VERMONT ORGANICS INFANT FORMULA
147 IND. PARK RD, GEORGIA, VT 05468

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL 02FTP

* A SOURCE OF ARACHIDONIC ACID (ARA)
** A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)

Questions or Comments: 1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

life's DHA•ARA™

life's DHA•ARA™ is a trademark of Martek Biosciences Corporation.

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USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, Vermont Organics™ ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ ORGANIC meets all USDA organic certification requirements. In addition to containing sources of organic fat, protein and carbohydrate, Vermont Organics™ ORGANIC is produced without the use of antibiotics, added growth hormones or potentially harmful pesticides.

L199-0730-0351

IMPORTANT NOTICE: BREAST MILK IS BEST FOR BABIES. Before using an infant formula, ask the advice of your health-care professional. This organic soy infant formula powder is free of lactose and cow's milk protein. It is intended to meet the nutritional needs of term infants and babies who are sensitive to lactose or those who do not consume milk protein or milk products. **Powdered infant formulas are NOT sterile and should NOT be fed to premature infants or infants who might have immune problems unless directed and supervised by your baby's doctor.**

DIRECTIONS FOR PREPARATION AND USE

Your baby's health depends on carefully following these preparation, use and storage instructions; changes could affect your baby's nutrition and safety. Before preparing the infant formula, make sure to always wash your hands. Clean can top before opening. **Ask your baby's doctor about the need to boil or sterilize water for formula and the proper preparation of bottle and feeding utensils.**

1. Pour desired amount of warm water (approx. 100°F/40°C) into bottle. (See Feeding Chart below.)
2. Add powder. Always add powder to water.
3. Cap bottle and shake well until powder is dissolved. Feed immediately. Discard any remaining formula in bottle after 1 hour from start of feeding.

Use this Feeding Chart for proper amount of water and powder.

To Make	Water	Powder (Use scoop enclosed to measure)
2 fl oz bottle	2 fl oz	1 unpacked level **scoop** (8.8 g)
4 fl oz bottle	4 fl oz	2 unpacked level **scoops** (17.6 g)
6 fl oz bottle	6 fl oz	3 unpacked level **scoops** (26.4 g)
8 fl oz bottle	8 fl oz	4 unpacked level **scoops** (35.2 g)
1 quart	29 fl oz	1 unpacked level standard measuring **cup** & 2 unpacked level **scoops** (125 g)

Storage: Store unused prepared bottled formula in the refrigerator at 35-40°F (2-4°C); **use within 24 hours.** DO NOT FREEZE. Warm infant formula to room temperature and shake well before feeding. Prepared formula should not be without refrigeration more than 2 hours. Store open and unopened cans in a dry area at room temperature. Cover the opened can tightly with plastic cap; use contents within 1 month. Avoid any extreme temperatures.

Warning: Do not use microwave to prepare or warm formula. Serious burns may occur.

Filled by weight, not by volume. Contents may settle during shipment.

Contents yield approximately 187 fl oz of formula

Martek DHA

Las instrucciones en Español se encuentran al dorso de esta etiqueta.

Easy to Digest
Powder • Add Water

Vermont Organics™

For Babies
0-12 Months

soy organic infant formula

with iron

Soy-Based Nutrition

Lipids – DHA & ARA

Nutrients found naturally in mother's milk

- Milk-Free
- Lactose-Free
- No Potentially Harmful Pesticides

USDA ORGANIC

Pareve

MADE IN VERMONT

NET WT 25.75 OZ (1 LB 9.75 OZ) 730 g

INGREDIENTS: **ORGANIC** CORN SYRUP SOLIDS, **ORGANIC** SOY PROTEIN, **ORGANIC** PALM OLEIN OR PALM OIL, **ORGANIC** COCONUT OIL, **ORGANIC** HIGH OLEIC (SAFFLOWER OR SUNFLOWER) OIL, **ORGANIC** SOY OIL, **AND LESS THAN 1%:** MORTIERELLA ALPINA OIL*, CRYPTHECODINIUM COHNII OIL**, ASCORBYL PALMITATE, L-CARNITINE, L-METHIONINE, MIXED TOCOPHEROL CONCENTRATE, SOY LECITHIN, TAURINE, CALCIUM CHLORIDE, CALCIUM PHOSPHATE, CUPRIC SULFATE, FERROUS SULFATE, MAGNESIUM CHLORIDE, MANGANESE SULFATE, POTASSIUM BICARBONATE, POTASSIUM CHLORIDE, POTASSIUM CITRATE, POTASSIUM HYDROXIDE, POTASSIUM IODIDE, SODIUM CITRATE, SODIUM SELENITE, ZINC SULFATE, ASCORBIC ACID, BETA-CAROTENE, BIOTIN, CALCIUM PANTOTHENATE, CHOLINE BITARTRATE, CYANOCOBALAMIN, FOLIC ACID, INOSITOL, NIACINAMIDE, PYRIDOXINE HYDROCHLORIDE, RIBOFLAVIN, THIAMINE HYDROCHLORIDE, VITAMIN A PALMITATE, VITAMIN D (CHOLECALCIFEROL), VITAMIN E (dl-ALPHA TOCOPHERYL ACETATE), VITAMIN K (PHYTONADIONE).
CONTAINS SOY INGREDIENTS.

Diluted: Each 5 fl oz (150 mL) contains 100 Calories

NUTRIENTS:	PER 100 CALORIES:
PROTEIN g	2.5
FAT g	5.3
CARBOHYDRATE g	10.6
WATER g	134
LINOLEIC ACID mg	750
VITAMINS:	
VITAMIN A IU	300
VITAMIN D IU	60
VITAMIN E IU	2
VITAMIN K mcg	8
THIAMINE (VITAMIN B_1) mcg	80
RIBOFLAVIN (VITAMIN B_2) mcg	90
VITAMIN B_6 mcg	60
VITAMIN B_{12} mcg	0.3
NIACIN mcg	1000
FOLIC ACID (FOLACIN) mcg	16
PANTOTHENIC ACID mcg	500

VITAMINS:	PER 100 CALORIES:
BIOTIN mcg	3
VITAMIN C (ASCORBIC ACID) mg	12
CHOLINE mg	24
INOSITOL mg	6
MINERALS:	
CALCIUM mg	105
PHOSPHORUS mg	69
MAGNESIUM mg	11
IRON mg	1.8
ZINC mg	1.2
MANGANESE mcg	25
COPPER mcg	75
IODINE mcg	15
SELENIUM mcg	2.8
SODIUM mg	36
POTASSIUM mg	120
CHLORIDE mg	80

DISTRIBUTED BY:
VERMONT ORGANICS INFANT FORMULA
147 IND. PARK RD, GEORGIA, VT 05468

CERTIFIED ORGANIC BY QUALITY ASSURANCE INTERNATIONAL 02FTP

* A SOURCE OF ARACHIDONIC ACID (ARA) ** A SOURCE OF DOCOSAHEXAENOIC ACID (DHA)
Ⓤ PAREVE Contains no dairy ingredients. Manufactured on dairy equipment.

Questions or Comments:
1-800-538-7615
9:00 a.m. to 5:00 p.m. EST
Monday – Friday

Produced under an ISO-9001 Quality System.

All infant formulas sold in the U.S. are required to be manufactured in accordance with, and meet the nutritional requirements of, the Federal Food, Drug and Cosmetic Act for infant formula under the regulation of the U.S. Food and Drug Administration.

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USE BEFORE DATE ON BOTTOM OF CAN

Breast milk is best. But if you decide to supplement breastfeeding with formula or formula-feed exclusively, and lactose-sensitivity is a concern, Vermont Organics™ Soy ORGANIC Infant Formula is a wholesome choice for your baby.

Made in the heart of the Green Mountains, Vermont Organics™ Soy ORGANIC meets all USDA organic certification requirements. A milk-free, lactose-free baby formula containing organic soy protein.

L188-0730-0351

Material Safety Data Sheet

Creation Date 08-Apr-2010 **Revision Date** 08-Apr-2010 **Revision Number** 1

1. PRODUCT AND COMPANY IDENTIFICATION

Product Name **Inositol**

Cat No. **AC122260000; AC122260010; AC122260050; AC122260051; AC122261000; AC122265000**

Synonyms Cyclohexanehexol; Hexahydroxycyclohexane

Recommended Use Laboratory chemicals

Company
Fisher Scientific
One Reagent Lane
Fair Lawn, NJ 07410
Tel: (201) 796-7100

Entity / Business Name
Acros Organics
One Reagent Lane
Fair Lawn, NJ 07410

Emergency Telephone Number
For information in the US, call: 800-ACROS-01
For information in Europe, call: +32 14 57 52 11

Emergency Number, Europe: +32 14 57 52 99
Emergency Number, US: 201-796-7100

CHEMTREC Phone Number, US: 800-424-9300
CHEMTREC Phone Number, Europe: 703-527-3887

2. HAZARDS IDENTIFICATION

CAUTION!

Emergency Overview

May cause skin, eye, and respiratory tract irritation. The toxicological properties have not been fully investigated.

Appearance White **Physical State** Solid **odor** odorless

Target Organs None known.

Potential Health Effects

Acute Effects

Principle Routes of Exposure

Eyes	May cause irritation.
Skin	May cause irritation.
Inhalation	May cause irritation of respiratory tract.
Ingestion	May cause irritation.

Chronic Effects None known.

See Section 11 for additional Toxicological information.

Aggravated Medical Conditions No information available.

3. COMPOSITION/INFORMATION ON INGREDIENTS

Haz/Non-haz

Component	CAS-No	Weight %
myo-Inositol	87-89-8	>95

4. FIRST AID MEASURES

Eye Contact Rinse immediately with plenty of water, also under the eyelids, for at least 15 minutes. Obtain medical attention.

Skin Contact Wash off immediately with plenty of water for at least 15 minutes. Get medical attention immediately if symptoms occur.

Inhalation Move to fresh air. If breathing is difficult, give oxygen. Get medical attention immediately if symptoms occur.

Ingestion Do not induce vomiting. Obtain medical attention.

Notes to Physician Treat symptomatically.

5. FIRE-FIGHTING MEASURES

Flash Point	No information available.
Method	No information available.
Autoignition Temperature	No information available.
Explosion Limits	
Upper	No data available
Lower	No data available
Suitable Extinguishing Media	Use water spray, alcohol-resistant foam, dry chemical or carbon dioxide.
Unsuitable Extinguishing Media	No information available.
Hazardous Combustion Products	No information available.
Sensitivity to mechanical impact	No information available.
Sensitivity to static discharge	No information available.

Specific Hazards Arising from the Chemical
Keep product and empty container away from heat and sources of ignition

Protective Equipment and Precautions for Firefighters
As in any fire, wear self-contained breathing apparatus pressure-demand, MSHA/NIOSH (approved or equivalent) and full protective gear.

NFPA	Health 1	Flammability 1	Instability 0	Physical hazards N/A

6. ACCIDENTAL RELEASE MEASURES

Personal Precautions Ensure adequate ventilation. Use personal protective equipment. Avoid dust formation.

Environmental Precautions Should not be released into the environment.

Methods for Containment and Clean Up Sweep up or vacuum up spillage and collect in suitable container for disposal. Avoid dust formation.

7. HANDLING AND STORAGE

Handling Wear personal protective equipment. Ensure adequate ventilation. Avoid contact with skin, eyes and clothing. Avoid ingestion and inhalation. Avoid dust formation.

Storage Keep containers tightly closed in a dry, cool and well-ventilated place.

8. EXPOSURE CONTROLS / PERSONAL PROTECTION

Engineering Measures Ensure that eyewash stations and safety showers are close to the workstation location. Ensure adequate ventilation, especially in confined areas.

Exposure Guidelines This product does not contain any hazardous materials with occupational exposure limits established by the region specific regulatory bodies.

NIOSH IDLH: *Immediately Dangerous to Life or Health*

Personal Protective Equipment

Eye/face Protection Wear appropriate protective eyeglasses or chemical safety goggles as described by OSHA's eye and face protection regulations in 29 CFR 1910.133 or European Standard EN166.

Skin and body protection Wear appropriate protective gloves and clothing to prevent skin exposure.

Respiratory Protection Follow the OSHA respirator regulations found in 29 CFR 1910.134 or European Standard EN 149. Use a NIOSH/MSHA or European Standard EN 149 approved respirator if exposure limits are exceeded or if irritation or other symptoms are experienced.

9. PHYSICAL AND CHEMICAL PROPERTIES

Physical State	Solid
Appearance	White
odor	odorless
Odor Threshold	No information available.
pH	No information available.
Vapor Pressure	No information available.
Vapor Density	No information available.
Viscosity	No information available.
Boiling Point/Range	No information available.
Melting Point/Range	220 - 228°C / 428 - 442.4°F

9. PHYSICAL AND CHEMICAL PROPERTIES

Decomposition temperature	No information available.
Flash Point	No information available.
Evaporation Rate	No information available.
Specific Gravity	No information available.
Solubility	Soluble in water
log Pow	No data available
Molecular Weight	180.16
Molecular Formula	C6 H12 O6

10. STABILITY AND REACTIVITY

Stability	Stable under normal conditions.
Conditions to Avoid	Incompatible products. Excess heat. Avoid dust formation.
Incompatible Materials	Strong oxidizing agents
Hazardous Decomposition Products	Carbon monoxide (CO), Carbon dioxide (CO_2)
Hazardous Polymerization	Hazardous polymerization does not occur.
Hazardous Reactions .	None under normal processing..

11. TOXICOLOGICAL INFORMATION

Acute Toxicity

Component Information

Component	LD50 Oral	LD50 Dermal	LC50 Inhalation
myo-Inositol	10 g/kg (Mouse)	Not listed	Not listed

Irritation	No information available.
Toxicologically Synergistic Products	No information available.

Chronic Toxicity

Carcinogenicity	There are no known carcinogenic chemicals in this product
Sensitization	No information available.
Mutagenic Effects	No information available.
Reproductive Effects	No information available.
Developmental Effects	No information available.

Teratogenicity No information available.

Other Adverse Effects See actual entry in RTECS for complete information. The toxicological properties have not been fully investigated..

Endocrine Disruptor Information No information available

12. ECOLOGICAL INFORMATION

Ecotoxicity

Do not empty into drains

Persistence and Degradability No information available

Bioaccumulation/ Accumulation No information available

Mobility .

Component	log Pow
myo-Inositol	-2.08

13. DISPOSAL CONSIDERATIONS

Waste Disposal Methods Chemical waste generators must determine whether a discarded chemical is classified as a hazardous waste. Chemical waste generators must also consult local, regional, and national hazardous waste regulations to ensure complete and accurate classification.

14. TRANSPORT INFORMATION

DOT Not regulated

TDG Not regulated

IATA Not regulated

IMDG/IMO Not regulated

15. REGULATORY INFORMATION

International Inventories

Component	TSCA	DSL	NDSL	EINECS	ELINCS	NLP	PICCS	ENCS	AICS	CHINA	KECL
myo-Inositol	X	X	-	201-781-2	-		X	X	X	X	KE-21013 X

Legend:
X - Listed
E - Indicates a substance that is the subject of a Section 5(e) Consent order under TSCA.
F - Indicates a substance that is the subject of a Section 5(f) Rule under TSCA.
N - Indicates a polymeric substance containing no free-radical initiator in its inventory name but is considered to cover the designated polymer made with any free-radical initiator regardless of the amount used.
P - Indicates a commenced PMN substance
R - Indicates a substance that is the subject of a Section 6 risk management rule under TSCA.
S - Indicates a substance that is identified in a proposed or final Significant New Use Rule
T - Indicates a substance that is the subject of a Section 4 test rule under TSCA.
XU - Indicates a substance exempt from reporting under the Inventory Update Rule, i.e. Partial Updating of the TSCA Inventory Data Base Production and Site Reports (40 CFR 710(B).
Y1 - Indicates an exempt polymer that has a number-average molecular weight of 1,000 or greater.
Y2 - Indicates an exempt polymer that is a polyester and is made only from reactants included in a specified list of low concern reactants that comprises one of the eligibility criteria for the exemption rule.

U.S. Federal Regulations

TSCA 12(b) Not applicable

SARA 313
Not applicable

SARA 311/312 Hazardous Categorization

Acute Health Hazard	No
Chronic Health Hazard	No
Fire Hazard	No
Sudden Release of Pressure Hazard	No
Reactive Hazard	No

Clean Water Act
Not applicable

Clean Air Act
Not applicable

OSHA
Not applicable

CERCLA
Not Applicable

California Proposition 65
This product does not contain any Proposition 65 chemicals.

State Right-to-Know
Not applicable

U.S. Department of Transportation

Reportable Quantity (RQ):	N
DOT Marine Pollutant	N
DOT Severe Marine Pollutant	N

U.S. Department of Homeland Security
This product does not contain any DHS chemicals.

Other International Regulations

Mexico - Grade No information available

Canada

This product has been classified in accordance with the hazard criteria of the Controlled Products Regulations (CPR) and the MSDS contains all the information required by the CPR.

WHMIS Hazard Class
Non-controlled

16. OTHER INFORMATION

Prepared By
Regulatory Affairs
Thermo Fisher Scientific
Tel: (412) 490-8929

Creation Date 08-Apr-2010

Print Date 08-Apr-2010

Revision Summary "***", and red text indicates revision

Disclaimer
The information provided on 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 guide for safe handling, use, processing, storage, transportation, disposal and release and is not to be considered as 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 material or in any process, unless specified in the text.

End of MSDS

ubiquitous presence of choline in the food supply (Zeisel, 1994). However, whether the endogenous synthetic activity is sufficient to obviate a dietary requirement for choline in infants is open for question. Evidence supporting the possibility of choline being an essential nutrient for humans includes studies in which decreased plasma choline levels were found in malnourished humans fed choline-deficient diets (Chawla et al., 1989; Sheard et al., 1986) and evidence of liver dysfunction in the absence of a source of dietary choline (Sheard et al., 1986). Zeisel (1994) listed several other pieces of evidence to support at least a conditional essentiality for choline including corroborating *in vitro* studies using human cell lines and *in vivo* studies with animal models.

Kaminski et al. (1980) reported that rats parenterally fed choline-free diets developed fatty liver disease, elevated liver transaminases, and conjugated bilirubin, all of which were reversible upon choline repletion. Several other investigators have demonstrated that rats fed choline-free diets had reduced levels of carnitine in liver, heart, and skeletal muscle, which was attributed to deficiency in available methyl-groups required for carnitine synthesis (Carter & Frenkel, 1978; Corredor et al., 1967). Other researchers have suggested that choline-deficient animals are more likely to develop liver cancers (Chandar & Lombardi, 1988; Ghoshal et al., 1983; Ghoshal & Farber, 1984; Newberne & Rogers, 1986). Although the mechanism(s) by which dietary choline deficiency might contribute to the development of hepatocarcinoma are unknown, enhanced cellular proliferation (Shinozuka & Lombardi, 1980), increased levels of lipid peroxidation (Rushmore et al., 1984), and undermethylation of DNA (Dizik et al., 1991) have been suggested.

Zeisel et al. (1991) compared biochemical effects in adult humans fed diets with or without choline for several weeks and observed 30% decreases in plasma choline and PC concentrations, increased liver enzyme activity, and decreased serum cholesterol levels in the choline-deficient group. Zeisel (1994) hypothesized that choline deficiency induced hepatic steatosis (fatty infiltration of the liver) by a disruption in liver transport mechanisms for triglycerides (as components of lipoproteins). Buchman et al. (1993) showed that low plasma free choline concentrations in patients receiving long-term parenteral nutrition is associated with hepatocellular enzyme abnormalities and that the plasma and RBC phospholipid membrane choline levels were normal in most of these patients. The causal mechanisms of liver injury in association with choline deficiency remain unclear, although this process appears to be reversible.

Oral administration of PC and the addition of choline to parenteral nutrition fluids administered to malnourished patients has been shown to prevent the hepatic dysfunction observed with choline deficiency (Buchman et al., 1992, 1995). Collectively, the results of clinical studies conducted in hospitalized patients have contributed to the contention that choline is a conditionally essential nutrient for patients receiving long-term parenteral nutrition.

Relatively little information exists to support a specific requirement for choline in healthy infants. Several studies have examined the content of choline in human milk. A limitation of these reports is that they did not include measurement of all available sources of choline (free choline, PC, and sphingomyelin) and did not control for stage of lactation or time of feeding (hindmilk has a higher concentration of choline than milk during earlier periods of a given feeding) (Zeisel, 1981).

The Expert Panel was unaware of any studies designed since 1985 that have addressed nutritional and toxicological aspects of choline in infant formula. The safety of choline administration has not been thoroughly assessed in infants. Adult studies have demonstrated that oral ingestion of choline at levels up to 6 g/d was without apparent untoward effects (Chawla et al., 1989).

Conclusions and recommendations. **The Expert Panel recommended a minimum content of choline in infant formulas of 7 mg/100 kcal based on limited available information on the lower end of the range for the choline content of human milk.** A dietary requirement for choline has been demonstrated for several species of mammals, but not for humans. Because of their greater rate of growth, it seems likely that the need of the infant for dietary choline may be greater than at other stages of development. Further studies will be required to refine our understanding of the choline requirement in infants.

The Expert Panel recommended a maximum content of choline in infant formulas of 30 mg/100 kcal. This recommendation was based on an extrapolation from adult data on the safe level of intake and allows for potential age-related differences in metabolism.[7]

Inositol

Background. Inositol (*myo*-inositol) is a six carbon, cyclic sugar-related alcohol that is abundant in many mammalian tissues. In plants and animals, inositol exists in its free form as phosphorylated lipid derivatives (phosphoinositides) and as glycosyl-phosphatidylinositol

[7] As noted, an intake of 6 g choline/d in adults was without apparent untoward effects (Chawla et al., 1989). In a 5-kg infant consuming approximately 500 kcal/d, that would be equivalent to 300 mg/100 kcal. The Expert Panel included an uncertainty factor of 10 to account for potential differences between adults and infants, thereby resulting in the maximum of 30 mg/100 kcal.

anchors of membrane lipids (Aukema & Holub, 1994). Scientific interest in inositol, particularly the polyphosphoinositides, has been heightened by the discovery of a role for these compounds as cellular mediators in signal transduction, growth, and metabolism regulation (Aukema & Holub, 1994; Holub, 1986).

In mammals, dietary sources of inositol are transported through the intestinal epithelium by energy and sodium-dependent mechanisms (Vilella et al., 1989). Once absorbed, inositol is distributed to the brain, liver, spleen, kidney, thyroid, and reproductive systems (Lewin et al., 1978). Serum inositol levels and the inositol pool in humans are tightly regulated primarily by renal metabolism and clearance mechanisms (Clements & Diethelm, 1979). The homeostasis of serum inositol levels in neonates has been shown to be primarily influenced by renal clearance mechanisms (Lewin et al., 1978).

In rats, endogenous synthesis of inositol from D-glucose occurs in testis, brain, liver, and kidney at rates which exceed the average level of dietary intake (Clements & Diethelm, 1979). It has been estimated that these tissues in humans also have the ability to synthesize inositol in considerable concentrations (Clements & Diethelm, 1979). Despite the capacity for endogenous synthesis at various sites, tissues concentrations of inositol are sensitive to fluctuations in dietary intake (Holub, 1986).

Foods of both plant and animal origin are rich in free and phosphorylated forms of inositol (Holub, 1986). In foods of animal origin, inositol is available as both the free form and as inositol phospholipid, whereas the predominant form of inositol in plants exists as phytate, a compound known to influence the bioavailability of many essential nutrients, including the divalent cations calcium, zinc, and iron (Aukema & Holub, 1994). It is because of the question of bioavailability that the current CFR recommendations include the stipulation that inositol be added at 4 mg/100 kcal to non milk-based formulas only. Conventional liquid formula preparations have been shown to contain between 35 and 70 mg free inositol/100 kcal (Indyk & Woollard, 1994).

Several reports include measurements of inositol content of human milk. Using gas chromatography, Ogasa et al. (1975) reported a mean *myo*-inositol content of mature milk (from an unspecified number of women) of 149 mg/L or 22 mg/100 kcal. Bromberger & Hallman (1986) also used gas chromatography to measure inositol concentrations of mature milk (also from an unspecified number of women) and reported a mean concentration of 1.81 mM or approximately 48 mg/100 kcal. Pereira et al. (1990) measured inositol content with an enzymatic fluorometric method and reported a mean inositol content (n=8 women delivering at term) of 1460 µmol/L or about 40 mg/100 kcal. In all studies containing data on temporal changes, inositol concentrations were noted to decrease over the course of lactation.

The range of milk-free inositol concentrations in the various reports can be attributed to differences in methodologies utilized. Earlier research methodologies utilized enzymatic, microbial and gas chromatographic methods of assessment while recent studies have utilized high performance liquid chromatographic techniques which have been shown to provide high levels of accuracy (Indyk & Woollard, 1994).

The FDA currently specifies a minimum inositol level of 4 mg/100 kcal only for nonmilk-based formulas (FDA, 1985a). A maximum value for inositol is not specified. No other authoritative body currently specifies a minimum or maximum inositol content for infant formulas (see Appendix A).

Review of extant data. Because of its endogenous synthetic capabilities, inositol has not been listed as an essential nutrient in the RDA for humans (NRC, 1989). As the synthesis and degradation of inositol are regulated *in vivo*, only under certain circumstances does it appear that inositol is an essential nutrient. Despite the capacity for endogenous synthesis, several clinical conditions have been identified in which inositol metabolism is impaired thereby raising the prospect of therapeutic efficacy from supplementation (Aukema & Holub, 1994). Diabetes mellitus and chronic renal failure are examples of such conditions in which altered inositol metabolism may account for organ dysfunction and disorders of the nervous tissues (Clements & Diethelm, 1979; Haneda et al., 1990; Holub, 1986; Olgemöller et al., 1990).

The finding of high inositol levels in human milk and in the developing fetus suggests that fetal and newborn development may represent a period of potential susceptibility to dietary deficiency (Aukema & Holub, 1994). Interest in the importance of inositol in the developing fetus and infant has been based on its role in the synthesis of phosphatidylglycerol, a primary component of lung surfactant. The synthesis and secretion of surfactant is a major regulatory feature of lung development, and its deficiency results in significant impairment of respiratory function (respiratory distress syndrome), a condition commonly associated with prematurity in infants. A potential benefit of inositol supplementation on surfactant production and lung development has been reported in both animals (Anceschi et al., 1988) and premature infants (Hallman et al., 1986, 1987, 1992). Fetal serum inositol levels have been found to be 3- to 20-fold higher than in adults and 2- to 10-fold higher than in term infants, thereby suggesting that the maintenance of high serum inositol levels may play an

important role in growth and maturation (Bromberger & Hallman, 1986). The relevance of these findings to healthy term infants and their dietary needs for inositol is not presently known.

The focus of nutritional research regarding inositol has been on the impact of changes in dietary intake on circulating and free inositol and phospholipid levels and the determination of the basis for the development of liver and intestinal lipodystrophy as a result of dietary deficiency of inositol (Holub, 1986). Animal models, e.g., rats and gerbils, have been shown to have markedly elevated triacylglycerol and esterified cholesterol levels in response to inositol-deficient diets (Andersen & Holub, 1976, 1980; Burton et al., 1976, Hayashi et al., 1974). Diets deficient in inositol have been associated with fatty infiltration of liver and intestines, presumably as a result of the promotion of fatty acid synthetic enzyme expression or the mobilization of fatty acids from adipose tissue (Beach & Flick, 1982; Hayashi et al., 1974). However, Burton et al. (1976) reported that neonatal rats fed inositol-free diets exhibited no impairment in growth, fatty liver infiltration, or impairment of central nervous system myelination despite diminished plasma and liver inositol concentrations. Burton et al. (1976) concluded that synthetic abilities of the newborn animal were sufficient to maintain proper cellular and organ function in spite of dietary deficiency.

Free inositol levels are noted to be higher in newborn infants than in adults and are influenced by diet (Bromberger & Hallman, 1986; Pereira et al., 1990). In a study evaluating the effect of diet on preterm infant serum inositol levels, breast-fed infants had substantially higher levels of inositol during the first three weeks of life than those fed infant formula or receiving parenteral nutrition (Pereira et al., 1990).

To date, no studies have been conducted to evaluate the impact of dietary inositol on growth and development of healthy term infants. Similarly, no studies examining the safety of inositol supplementation have been reported in humans.

Conclusions and recommendations. **The Expert Panel recommended a minimum content of *myo*-inositol in infant formulas of 4 mg/100 kcal.** Although the essentiality of dietary *myo*-inositol for infants remains an open question, it is an essential nutrient for at least two other species of mammals. Until more data on the requirement for *myo*-inositol are available, it seems prudent to reaffirm the CFR value of 4 mg/100 kcal.

The Expert Panel recommended a maximum content of *myo*-inositol in infant formulas of 40 mg/100 kcal. Although current usage data are not available, this value is near the upper limit reported for human milk.

VI. POTENTIAL RENAL SOLUTE LOAD (PRSL)

BACKGROUND

Substances that require excretion by the kidneys are referred to collectively as the renal solute load (RSL). Under most circumstances, the renal solute load is closely related to the nitrogen and electrolyte content of the diet. To excrete these by-products, a certain amount of water is required, thus, contributing to the net balance of water. As the renal solute load increases, or as the available water for urine formation decreases, the osmolar concentration of the urine must also increase.

Potential renal solute load (PRSL) refers to solutes of dietary origin that would need to be excreted in the urine if none were diverted into synthesis of new tissues and none were lost through nonrenal routes, such as through the feces or skin. Under most circumstances, urea, chloride, potassium, phosphorus and sodium contribute more than 90% of the RSL (Fomon & Ziegler, 1993). The following equation may be used for the derivation of the PRSL:

$$PRSL = N/28 + Na + Cl + K + P_a$$

where N = nitrogen (milligram), Na = sodium, Cl = chloride, K = potassium, and P_a = available (nonphytate) phosphorus.

Dietary intakes of solutes are expressed as mmol (or mosmol) and the factor N/28 represents excretion of nitrogenous substances (with the assumption that the modal number of nitrogen atoms per molecule is 2).

The PRSL of human milk has been determined to be 14 mosmol/100 kcal, as opposed to conventional cow milk formulas, soy protein-based formulas[8] and whole cow milk which are approximately 20, 26 and 46 mosmol/100 kcal, respectively (Fomon & Ziegler, 1993).

REVIEW OF EXTANT DATA

Ziegler & Fomon (1989) reviewed the epidemiologic data and noted that infants fed formulas providing a PRSL of 39 mosmol/100 kcal or more (commonly found in evaporated milk formulas that were used for feeding infants

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[8] The Expert Panel recognized that approximately 50% of the phosphate in soy protein isolates and, consequently, 30% of the phosphorus in soy protein-based formulas, is complexed as phytate. This phytate-associated phosphorus is generally not available for biological activity and thus is not a contributor toward the PRSL. Therefore, for the purposes of this report, the Expert Panel considered available phosphorus or nonphytate phosphorus (P_a) the measured total phosphorus, less the measured phytate-associated phosphorus.

Nutrient Requirements For Preterm Infant Formulas[1,2,3]

Catherine J. Klein,[4] Editor

Life Sciences Research Office, 9650 Rockville Pike, Bethesda, Maryland 20814

ABSTRACT Achieving appropriate growth and nutrient accretion of preterm and low birth weight (LBW) infants is often difficult during hospitalization because of metabolic and gastrointestinal immaturity and other complicating medical conditions. Advances in the care of preterm-LBW infants, including improved nutrition, have reduced mortality rates for these infants from 9.6 to 6.2% from 1983 to 1997. The Food and Drug Administration (FDA) has responsibility for ensuring the safety and nutritional quality of infant formulas based on current scientific knowledge. Consequently, under FDA contract, an ad hoc Expert Panel was convened by the Life Sciences Research Office of the American Society for Nutritional Sciences to make recommendations for the nutrient content of formulas for preterm-LBW infants based on current scientific knowledge and expert opinion. Recommendations were developed from different criteria than that used for recommendations for term infant formula. To ensure nutrient adequacy, the Panel considered intrauterine accretion rate, organ development, factorial estimates of requirements, nutrient interactions and supplemental feeding studies. Consideration was also given to long-term developmental outcome. Some recommendations were based on current use in domestic preterm formula. Included were recommendations for nutrients not required in formula for term infants such as lactose and arginine. Recommendations, examples, and sample calculations were based on a 1000 g preterm infant consuming 120 kcal/kg and 150 mL/d of an 810 kcal/L formula. A summary of recommendations for energy and 45 nutrient components of enteral formulas for preterm-LBW infants are presented. Recommendations for five nutrient:nutrient ratios are also presented. In addition, critical areas for future research on the nutritional requirements specific for preterm-LBW infants are identified. J. Nutr. 132: 1395S-1577S, 2002.

PREFACE

The Life Sciences Research Office (LSRO) of the American Society for Nutritional Sciences (ASNS) provides scientific assessments of topics in the biomedical sciences. Reports are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine. This LSRO/ASNS report was developed for and supported in part by the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA) under Task Orders #11 & 13 of Contract No. 223-92-2185. During the course of this project, administrative responsibility for LSRO transitioned from the Federation of American Societies for Experimental Biology in 1998 through the ASNS to separate incorporation as LSRO, Inc in 2001. The ASNS acknowledges the cooperation of LSRO, Inc. in preparation of this report.

An Expert Panel provided scientific oversight and direction for all aspects of the project. The LSRO independently appointed members of the Panel based on their qualifications, experience, and judgment, with due considerations for balance and breadth in the appropriate professional disciplines. Notices in the *Federal Register* of November 15, 1996 and January 15, 1998, invited submission of data, information, and views bearing on the topic under study. LSRO held two Open Meetings, March 26, 1997 and March 27, 1998, and accepted written submissions. The Expert Panel convened six times (four full meetings and two conference calls) to assess the available data. Drs. William Heird, C. Lawrence Kien, Michael Georgieff, Ephraim Levin, and J. Cecil Smith made significant contributions to the writing and construct of sections of the report. Special appreciation is expressed to Dr. William Hay for his contributions during final review. Because the Committee on Nutrition of the American Academy of Pediatrics, the Food and Nutrition Board of the Institute of Medicine, and Health Canada provide professional advice on issues related to the topics of this report, these organizations received notices of progress of this study and opportunity for review. The LSRO staff, special consultants, and members of the Expert Panel considering all available information drafted the report, incorporated reviewers' comments and provided additional documentation and viewpoints for incorporation into the final report. The final report was reviewed and approved by the Expert Panel and the LSRO Board of Directors. On completion of these review procedures, the report was approved and transmitted to the FDA by the Executive Officer, ASNS, and the Executive Director, LSRO.

The listing of members of the Expert Panel and others who assisted in preparation of this report does not imply endorsement of all statements in the report. Although this is a report of the LSRO/ASNS, it does not necessarily reflect the opinion of the

[1]Prepared for the Center for Food Safety and Applied Nutrition, Food and Drug Administration, Department of Health and Human Services, Washington, DC 20204 under FDA Contract No. 223-92-2185, Task Orders #11 & #13. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commerical products, or organizations imply endorsement by the U.S. Government.

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[3]Reference citation for this online document is: Klein, C. J. Editor, Nutrient Requirements for Preterm Infant Formulas (2002). J. Nutr. 132(4) [serial online]. Available from url: http://www.nutrition.org/cgi/content/full/132/4/e1

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duodenum, the site where these perfusion studies were carried out (Antonowicz et al., 1974; Auricchio et al., 1965). A more extensive discussion of the digestion of glucose polymers appears in Appendix A.

As noted above, Griffin and Hansen (1999) showed that elimination of lactose from the formula and replacing it with maltose improved feeding tolerance in preterm infants. Although these investigators did not specifically address the merits of glucose polymer feeding, their results are germane to the issue of whether reduction or elimination of lactose in preterm infant formula may be relatively advantageous. Current commercial preterm infant formulas contain glucose polymers as a replacement for lactose. Because glucose polymers in present preterm infant formulas are probably digested in a manner similar to maltose (Gray, 1992; Kien et al., 1989), it is plausible that similar results to those of Griffin and Hansen (1999) would be observed if glucose polymers and not maltose were substituted for lactose. In fact, as pointed out in a letter to the editor (Kien, 2001), in a series of small, brief studies comparing a preterm infant formula containing 50% of the carbohydrate as lactose and glucose polymers with a similar formula containing lactose as the sole carbohydrate, weight gain was lower in the 100% lactose group (although not significantly so)(Kien et al., 1982; Kien et al., 1990a; Kien et al., 1998). However, in contrast to the Griffin and Hansen paper (1999), energy intake was also higher (but also, $P > 0.05$), implying that energy utilization could have been impaired.

Also, as discussed above, data are contradictory on the effect of lactose on calcium absorption, but it does appear that substitution of glucose polymers for lactose in preterm infants with defective lactose digestion may result in an improvement in calcium absorption. On the basis primarily of the results of Griffin and Hansen (1999), but supported apparently by casual observations on weight gain made in the course of studies of lactose digestion and absorption (Kien, 2001), reduction or elimination of lactose and replacement with more readily digestible carbohydrate such as maltose or glucose polymers may facilitate better feeding tolerance in preterm infants.

In summary, glucose polymers appear to be rapidly hydrolyzed and absorbed by the neonate, and the carbohydrate energy not absorbed in the small intestine is rapidly salvaged by colonic bacteria. In the lactase-deficient preterm infant, substitution of glucose polymers for lactose may enhance calcium absorption. Finally, substitution of lactose in formulas with maltose (and by inference, based on the mode of digestion, also glucose polymers) may improve feeding intolerance in preterm infants.

Recommendations

Note. **The Expert Panel found no evidence to justify a specific recommendation for glucose polymers or maltose per se in preterm infant formula. However, the use of these carbohydrates (or potentially other more readily digestible carbohydrates) as a partial alternative to lactose may have beneficial effects.**

MYO-INOSITOL

Background

myo-Inositol (inositol) is a six-carbon, cyclic sugar-related alcohol that is abundant in mammalian tissues. In plants and animals, *myo*-inositol exists in its free form, as phosphorylated lipid derivatives (phosphoinositides), and as glycosylphosphatidylinositol, anchors of membrane lipids (Aukema & Holub, 1994). A novel glycoprotein containing *myo*-inositol has been identified in rat brain and may serve as a recognition molecule on neurons during development (Holub, 1992; Uauy et al., 1993). In addition to containing free *myo*-inositol, human milk contains a disaccharide form of *myo*-inositol, 6-β-galactinol (Holub, 1986; Holub, 1992; Uauy et al., 1993). Scientific interest in *myo*-inositol derivatives, particularly the polyphosphoinositides, has been heightened by the discovery of a major role for these compounds as cellular mediators of signal transduction and intracellular calcium regulation (Aukema & Holub, 1994; Holub, 1986).

In rats, endogenous synthesis of *myo*-inositol from D-glucose occurs in testis, brain, liver, and kidney (Hauser, 1963). Clements and Diethelm (1979) demonstrated that the human kidney also has the ability to synthesize *myo*-inositol. Despite this, tissue concentrations of *myo*-inositol in rodents are still sensitive to fluctuations related to dietary intake (Holub, 1986). After 2 weeks of life, serum *myo*-inositol concentrations in preterm-low birth weight (LBW) infants were correlated with *myo*-inositol intake (Bromberger & Hallman, 1986).

In mammals, dietary sources of *myo*-inositol are transported through the intestinal epithelium by energy-dependent and sodium-dependent mechanisms (Vilella et al., 1989). Once absorbed, *myo*-inositol is distributed to the brain, liver, spleen, kidney, thyroid, and reproductive systems (Lewin et al., 1978). Serum *myo*-inositol level and the *myo*-inositol pool in humans are regulated primarily by renal metabolism and clearance mechanisms (Clements & Diethelm, 1979). The homeostasis of serum *myo*-inositol levels in neonates has been shown to be primarily influenced by renal clearance (Lewin et al., 1978).

Rats have markedly elevated triacylglycerol and esterified cholesterol levels when fed *myo*-inositol-deficient diets (Andersen & Holub, 1976; Burton et al., 1976; Hayashi et al., 1974). Growing rats fed diets deficient in *myo*-inositol have been reported to exhibit fatty infiltration of the liver, presumably as a result of increased hepatic fatty acid synthesis or the mobilization of fatty acids from adipose tissues (Beach & Flick, 1982; Hayashi et al., 1974). In contrast, neonatal rats fed *myo*-inositol-restricted diets from 6 days of age and *myo*-inositol-free diets from 16 to 72 days of age exhibited no fatty infiltration of the liver and no impairment of central nervous system myelination, despite diminished plasma and liver *myo*-inositol concentrations (Burton et al., 1976). Growth was suboptimal in both the experimental and the control groups. These investigators concluded that *myo*-inositol synthetic abilities of newborn rats are sufficient to maintain proper cellular and organ function despite dietary deficiency.

As the synthesis and degradation of *myo*-inositol are regulated in vivo, only under unusual circumstances does the clinician give particular attention to the patient's intake of exogenous *myo*-inositol. These circumstances include certain clinical situations in which *myo*-inositol synthesis is impaired (Aukema & Holub, 1994). Diabetes mellitus and chronic renal failure are examples of conditions in which altered *myo*-inositol metabolism and excretion may result from specific organ system dysfunction (Clements & Diethelm, 1979; Haneda et al., 1990; Holub, 1986; Olgemöller et al., 1990).

An estimated one or two infants per 1000 births in North America are born with a neural tube defect (Rosenberg, 1997). Approximately 70% of these defects can be prevented by adequate maternal folate intake and status during the first month of pregnancy. The remaining 30% of cases occur independent of maternal folate status (van Straaten & Copp, 2001). The curly tail strain of mice has been considered a genetic model of human folate-resistant neural tube defects because of the following similarities: form and structure of the defects, axial location, sex bias, and elevated concentration of α-fetoprotein in amniotic fluid (Rosenberg, 1997; van

Straaten & Copp, 2001). In curly tail mice, a deficiency of *myo*-inositol increases the incidence of exencephaly, whereas administration of exogenous *myo*-inositol ameliorates this effect (van Straaten & Copp, 2001). Furthermore, injecting dams with *myo*-inositol during gestation reduces the frequency of spina bifida (Rosenberg, 1997). Some have suggested that the effects of *myo*-inositol may be mediated through increased action of protein kinase C (Rosenberg, 1997; van Straaten & Copp, 2001) and up-regulation of expression of retinoic acid receptor β in the hindgut (Rosenberg, 1997).

Dietary sources of myo-inositol

Most foodstuffs from both plant and animal sources are rich in free and phosphorylated forms of *myo*-inositol (Holub, 1986). In plants, the predominant forms of *myo*-inositol are phytates, which are compounds known to form complexes with divalent cations; this is mostly relevant for soy-based formulas that are not recommended for premature infants.

The concentration of *myo*-inositol in human milk is three to four times greater than that in cow milk (Indyk & Woollard, 1994; Ogasa et al., 1975). Myo-Inositol concentration in human milk up to 4 months postpartum varies widely, with studies reporting the following concentrations:

- 490 μmol of free *myo*-inositol/L (~13 mg/100 kcal) (Indyk & Woollard, 1994)
- 830 μmol of total inositol/L (~22 mg/100 kcal) (Ogasa et al., 1975)
- 1450 μmol of free *myo*-inositol/L (~38–39 mg/100 kcal) (Pereira et al., 1990)
- 1800 μmol of *myo*-inositol/L (~47–48 mg/100 kcal) (Bromberger & Hallman, 1986)

On average, 24-hour milk samples collected at 14 (n = 99), 42 (n = 99), and 89 (n = 25) days postpartum contained 642, 766, and 830 μmol of *myo*-inositol/L (~17–22 mg/100 kcal), respectively (Huisman et al., 1996). In summary, the concentration of *myo*-inositol in human milk ranges from about 13 to 48 mg/100 kcal.

The variation of *myo*-inositol concentrations in milk reported in the literature has been attributed to differences in analytical methodologies (Raiten et al., 1998a). As explained by Raiten et al. (1998a), earlier studies used enzymatic fluorimetric (Pereira et al., 1990), microbial, and gas-liquid chromatographic (Bromberger & Hallman, 1986) (Ogasa et al., 1975) assays. More recent studies have utilized high-performance liquid chromatography because of its high level of accuracy (Indyk & Woollard, 1994). A new method of ion chromatographic determination of *myo*-inositol in liquids was recently published (Tagliaferri et al., 2000).

The concentration of *myo*-inositol in human milk is similar for mothers of term and preterm infants up to 4 months of lactation (Bromberger & Hallman, 1986; Pereira et al., 1990) and decreases with time during the first 6 weeks postpartum (Ogasa et al., 1975; Pereira et al., 1990). Phosphatidylinositol content, both total concentration and as a percentage of phospholipid, was similar for mature milk from mothers of term and preterm infants (Bitman et al., 1984; Bromberger & Hallman, 1986).

For term infants, the *myo*-inositol content of infant formulas available in the Netherlands reportedly varied from 22 to 346 μmol/L (4–62 mg/L) (Huisman et al., 1996). The infant formulas available in New Zealand contain 23–65 mg of free *myo*-inositol/100 g (~1275–3600 μmol/L) and 38–77 mg of total inositol/100 g (~2100–4275 μmol/L) (Indyk & Woollard, 1994). Milk-based term infant formulas available in Switzerland contain 30–150 mg of total inositol/100 g (~1670–8300 μmol/L), similar to the range measured in soy-based infant formula, in which total inositol refers to the sum of free *myo*-inositol, inositol monophosphate, and *myo*-inositol derived from lecithin (Tagliaferri et al., 2000). The preterm formulas in the United States contain 5.5–17 mg/100 kcal (~270–760 μmol of *myo*-inositol/L) (Abbott Laboratories. Ross Products Division, 2001; Mead Johnson Nutritionals, 2000). An amino acid-based, hypoallergenic formula, not designed for preterm-LBW infants but sometimes used in the United States for such infants with food protein intolerance or allergy, contains 23.3 mg of *myo*-inositol/100 kcal (~5400 μmol of *myo*-inositol/L) (SHS North America, 2000).

Current recommendations for myo-inositol

The Code of Federal Regulations (CFR) specified a minimum of 4 mg of *myo*-inositol/100 kcal for non-milk-based infant formulas (Food and Drug Administration, 1985); no maximum concentration was indicated. The minimum was based on a recommendations of the American Academy of Pediatrics Committee on Nutrition (AAP-CON) (1976; 1985b), set in 1976 as 4 mg/100 kcal (22 μmol/100 kcal), to represent an average value of *myo*-inositol concentration in milk-based formulas at that time. Because evidence of *myo*-inositol deficiency was lacking, milk-based formula rather than human milk was used as the reference to set the minimum recommendation (American Academy of Pediatrics. Committee on Nutrition, 1976). Although the AAP-CON (1976) did not specify a maximum for *myo*-inositol, amounts equal to the amount found in human milk were permitted in infant formula.

The expert panel compiling the report *Assessment of Nutrient Requirements for Infant Formulas* (Raiten et al., 1998a) recommended a minimum *myo*-inositol content of 4 mg/100 kcal for term formula. That expert panel was unaware of any new evidence that would shed light on the question of the essentiality of *myo*-inositol, particularly for healthy term infants, and therefore accepted the 1985 specification of the CFR. The same expert panel recommended a maximum content of 40 mg of *myo*-inositol/100 kcal (~1500–1600 μmol/L) for term infant formulas. This upper limit was within the range of *myo*-inositol reported for mature human milk.

The European Society of Paediatric Gastroenterology and Nutrition (1991) made no recommendations for *myo*-inositol. The Association of the Food Industries for Particular Nutritional Uses of the European Union (1996) recommended that the minimum *myo*-inositol content of LBW formulas be 4.0 mg/100 kcal. Health Canada (1995) *Guidelines* made no recommendations for a minimum *myo*-inositol content but indicated that levels in formula should not exceed those found in mature human milk (2500 μmol/L or 65-67 mg/100 kcal).

Investigators have also recommended that preterm infant formula contain amounts of *myo*-inositol similar to that found in human milk (Hallman et al., 1992, Uauy et al., 1993), 1000–2500 μmol of *myo*-inositol/L (Uauy et al., 1993) (26–67 mg/100 kcal, assuming an energy content of 670–690 kcal/L).

Tissue concentrations of myo-inositol

The in vivo concentrations of *myo*-inositol in human cerebellum, as measured by magnetic resonance, did not differ among 12 preterm infants of 27–42 weeks postconceptional age, 8 preterm and term infants of 31–45 weeks postconceptional age, and 6 adults (Hüppi et al., 1991).

The concentration of free *myo*-inositol in cerebrospinal fluid of both term and preterm infants is elevated in the perinatal period (Burgi & Caldwell, 1975). The concentrations then decline to levels similar to adults by 12 months of age.

Blood concentrations of *myo*-inositol are inversely corre-

lated with gestational age (Hallman et al., 1985); plasma concentrations of *myo*-inositol are significantly higher during the first week of life in infants born at less than 31 weeks of gestational age than in infants of longer gestation (Carver et al., 1997). After birth, the plasma concentration of *myo*-inositol declines, at least until the preterm infant can tolerate 70 mL/kg or more of enteral formula (~15–28 days of life) (Carver et al., 1997). Plasma concentrations of *myo*-inositol were not significantly different between this time and hospital discharge (Carver et al., 1997). Plasma *myo*-inositol concentrations 2 months after discharge from the hospital were significantly lower than at discharge (Carver et al., 1997). Others (Friedman et al., 2000; Hallman et al., 1985; Hallman et al., 1987; Hallman et al., 1992) reported similar progressive declines in serum concentrations of *myo*-inositol in preterm infants from birth until 60 days of life, with substantial declines typically evident between birth and 3 days of life.

Some have speculated that high *myo*-inositol levels in cord blood might indicate a higher requirement for *myo*-inositol in prenatal development (Raiten et al., 1998a). Because serum samples from preterm infants contain *myo*-inositol levels that are higher than levels in adults and term infants and *myo*-inositol levels in human milk are relatively high, questions have also been raised about the neonatal requirement (Burton et al., 1976). Whether preterm-LBW infants have a higher requirement than term infants for endogenous and perhaps exogenous *myo*-inositol for optimal development is not known (Raiten et al., 1998a). If this were true, the perinatal period would be a period of potential susceptibility to dietary *myo*-inositol deficiency (Aukema & Holub, 1994).

The serum *myo*-inositol level, adjusted for gestational age, was significantly higher during the first 12 hours of life for infants with respiratory distress syndrome compared with those infants with no lung disease (Hallman et al., 1985). Yet among the infants with respiratory distress syndrome, those with lower serum *myo*-inositol tended to have more severe respiratory distress (Hallman et al., 1985). Hallman et al. (1992) determined that the serum *myo*-inositol concentration averaged 298 μmol/L in the first week postpartum for preterm infants who developed lung or eye disease and/or died. In contrast, the serum *myo*-inositol value averaged 496 μmol/L in the first week postpartum for preterm infants without serious morbidity. Similarly, Friedman et al. (2000) reported that 37 preterm infants who developed retinopathy had an average serum *myo*-inositol concentration of 280 μmol/L during the first 3 days of life compared with an average of 415 μmol/L for 51 infants who did not develop retinopathy. Hallman et al. (1992) suggested that serum *myo*-inositol concentrations lower than 380 μmol/L in the first week of life were associated with an increased risk of retinopathy, respiratory failure, and death. Using regression techniques to adjust for *myo*-inositol intake, duration of oxygen therapy, and birth weight, Friedman et al. (2000) determined that each decrease of 100 μmol/L in serum *myo*-inositol concentration produced greater than a four-fold increase in the odds of developing severe retinopathy of prematurity.

The blood concentrations of free *myo*-inositol in neonates are influenced by diet (Bromberger & Hallman, 1986; Pereira et al., 1990). Five preterm infants fed human milk containing an average of 1456 μmol of *myo*-inositol/L (~38–39 mg/100 kcal) had serum *myo*-inositol levels of 232–250 μmol/L during the third to fifth weeks of life (Pereira et al., 1990). These values were significantly higher than the 125–150 μmol/L reported for five preterm infants fed formula containing 420 μmol/L (~9 mg/100 kcal).

Myo-inositol supplementation

Special interest has been aroused by the knowledge of the role played by *myo*-inositol in the synthesis of phosphatidylglycerol, a primary component of lung surfactant. The synthesis and secretion of surfactant are major regulatory features of lung development. A disorder of these processes leads to respiratory distress syndrome, a significant impairment of respiratory function commonly associated with prematurity in humans.

myo-Inositol supplementation has had beneficial effects on respiratory distress syndrome and bronchopulmonary dysplasia, particularly in conjunction with other therapies (Anceschi et al., 1988; Hallman et al., 1986; 1987; 1990; Hallman et al., 1992) (Howlett & Ohlsson, 2001).

The incidence of retinopathy, particularly severe retinopathy, is significantly reduced by *myo*-inositol supplementation ranging from 80 mg/kg for the first 5 days of life to about 68 mg/kg daily until within 1 week of discharge from the hospital, delivered in formula containing 44.4 mg/100 kcal (Hallman et al., 1990; Hallman et al., 1992, Howlett & Ohlsson, 2001). Preterm-LBW infants with a serum *myo*-inositol concentration of less than 215 μmol/L after 30 days postpartum were four to six times more likely to develop severe retinopathy if they consumed infant formula containing 242 μmol of *myo*-inositol/L (5.4 mg/100 kcal) during hospitalization than if their formula contained 2500 μmol/L (44 mg/100 kcal, at an energy intake of 30 kcal/fl oz) (Friedman et al., 2000). Because of potential benefit for the retinal and respiratory conditions, Hallman et al. (1992) recommended that formula for preterm infants provide amounts of *myo*-inositol equal to that in breast milk (13-48 mg/100 kcal).

Howlett and Ohlsson (2001) conducted a systematic review and meta-analysis of studies that tested the effect of *myo*-inositol on respiratory distress syndrome in preterm infants. The occurrence of intraventricular hemorrhage, grade III-IV, was significantly decreased (RR 0.55, 95% CI 0.32, 0.95; RD −0.09, 95% CI −0.17, -0.01) and mortality was also significantly reduced (RR 0.48, 95% CI 0.28, 0.80; RD −0.131, 95% CI −0.218, -0.043) in those preterm-LBW infants supplemented with *myo*-inositol. In contrast, sepsis and necrotizing enterocolitis appear to be unaffected by dietary intake of *myo*-inositol (Howlett & Ohlsson, 2001). Future multicenter randomized controlled trials of *myo*-inositol supplementation are encouraged to confirm reported benefits (Howlett & Ohlsson, 2001).

Toxicity

Uauy et al. (1993) speculated that a large intake of *myo*-inositol might cause diuresis, leading to fluid loss and, potentially, dehydration. However, indices of hematological, renal, and liver function did not change after oral administration of 12 g of *myo*-inositol/d for 4 weeks to 13 adults diagnosed with major depressive disorder or bipolar affective disorder-depressed and to 12 physically healthy adults diagnosed with chronic schizophrenia (Levine et al., 1995; Levine, 1997). One patient complained of nausea and one of flatus (Levine, 1997). Benjamin et al. (1995) reported that an oral dose of 6 g of *myo*-inositol twice a day for 4 weeks resulted in minimal side effects in adults (2 of 21 adults complained of sleepiness). In nine children, an average of 5.6 years of age, who had a diagnosis of infantile autism, oral administration of 100 mg/kg of body weight twice a day for 4 weeks did not lead to any reported side effects (Levine et al., 1997). Specifically, there were no reported changes in appetite, no nausea, and no diarrhea (Levine et al., 1997). In 11 children older than 4 years with attention deficit disorder, oral administration of

myo-inositol at 100 mg/kg of body weight twice a day for 4 weeks did not lead to serious side effects, although a trend for aggravation of the syndrome was noted (Levine, 1997). Therefore, *myo*-inositol supplementation in physically healthy adults and children has been well tolerated.

Levine et al. (1995) and others (Holub, 1986) cautioned that conditions leading to severe hyperinositolemia, particularly renal failure, may be associated with reduced peripheral nerve conduction. Furthermore, is not known whether *myo*-inositol supplementation might increase fetal resorption in pregnant women.

Renal immaturity may impair the preterm neonate's ability to filter, catabolize, and excrete *myo*-inositol. Lewin et al. (1978) determined that preterm-LBW infants were capable of excreting in urine as much or more *myo*-inositol than they had ingested when intakes ranged from 5 to 36 mg of *myo*-inositol/d. However, renal excretion by preterm-LBW infants does not keep pace with daily *myo*-inositol intakes of 205 mg/kg. Under these circumstances, renal excretion of *myo*-inositol represents, on average, about 53% of intake (Hallman et al., 1987). Hallman et al. (1986) administered 40 mg of *myo*-inositol/kg intragastrically, or 75% of that amount intravenously when the enteral route was inaccessible, four times per day to preterm-LBW infants with adequate renal function beginning 12–48 hours postpartum and continuing for 10 days without any adverse effects. Friedman et al. (2000) fed preterm infants 44 mg of *myo*-inositol/100 kcal (68 mg/150 mL) until they weighed 1800–1900 g. They noted that there were no deleterious effects associated with this level of *myo*-inositol feeding.

Conclusions and recommendations

Minimum. The Expert Panel found no publications that identified a requirement for *myo*-inositol by preterm-LBW infants. The CFR specified a minimum of 4 mg of *myo*-inositol/100 kcal for non-milk-based infant formulas (Food and Drug Administration, 1985). Although current domestic preterm formulas are milk-based ones, hypoallergenic non-milk-based formulas may be developed for this population. The Expert Panel recommended the minimum *myo*-inositol concentration for preterm infant formula of 4 mg/100 kcal, as had previously been recommended for term infant formula (Raiten et al., 1998a).

Maximum. Because preterm-LBW infants with serum *myo*-inositol concentrations less than 215 μmol/L after 30 days postpartum were four to six times more likely to develop severe retinopathy if they consumed infant formula containing *myo-inositol* at 242 μmol/L (5.4 mg/100 kcal) during hospitalization than if their formula contained 2500 μmol/L (44 mg/100 kcal) (Friedman et al., 2000), supplementing formula with amounts of *myo*-inositol comparable to that found in human milk may be beneficial. On average, measures of human milk range from about 13 to 48 mg of *myo*-inositol/100 kcal.

Friedman et al. (2000) fed preterm infants 44 mg of *myo*-inositol/100 kcal (68 mg/150 mL) until they weighed 1800–1900 g without reports of adverse effects.

The Expert Panel recommended a maximum concentration of 44 mg/100 kcal for preterm infant formula, increased from the 40 mg/100 kcal as had previously been recommended for term infant formula (Raiten et al., 1998a). Further studies are needed to determine how much, if any, dietary *myo*-inositol leads to an improved outcome for preterm-LBW infants.

Recommendations

Minimum. **The Expert Panel recommended that the minimum *myo*-inositol content of preterm infant formula be 4 mg/100 kcal.**

Maximum. **The Expert Panel recommended that the maximum *myo*-inositol content of preterm infant formula be 44 mg/100 kcal.**

9. FAT

TOTAL FAT

Background

The absolute requirement of the human species for fat is limited to the amount of essential fatty acids necessary to ensure optimal fatty acid composition and function of growing tissues and for normal eicosanoid synthesis. At most, this requirement is no more than 5% of total energy intake. However, fat accounts for approximately 50% of the nonprotein energy content of both human milk and currently available infant formulas. This is thought to be necessary to ensure that total energy intake is adequate to support growth as well as optimal utilization of dietary protein (Fomon, 1993b).

In theory, the energy usually supplied by fat could be supplied as carbohydrate, from which all fatty acids except the essential fatty acids and their anabolic products can be synthesized. In practice, however, it is difficult to ensure sufficient energy intake without a fat intake considerably in excess of the requirement for essential fatty acids. Moreover, metabolic efficiency is greater if the total nonprotein energy intake is achieved with a mixture of dietary fat and carbohydrate rather than predominately carbohydrate. In addition, if the carbohydrate content of a high carbohydrate formula is supplied as simple carbohydrates (i.e., mono- and disaccharides), the resulting high osmolality is likely to produce diarrhea. Dietary fat also serves a useful role in facilitation of the absorption, transport, and delivery of fat-soluble vitamins, and it is an important satiety factor (Fomon, 1993a).

The total fat content of human milk, including that of mothers who deliver prematurely, varies considerably, but it usually accounts for 45–60% of the total energy content of the milk (Jensen, 1999). Fat also accounts for approximately 50% of the nonprotein energy content of current preterm infant formulas. These formulas contain a variety of vegetable oils as well as medium-chain triglyceride (MCT) to enhance fat absorption. In general, the mixture of oils in these formulas does not provide the same proportions of saturated, monosaturated, and polyunsaturated fatty acids as those found in human milk.

However, because the fatty acid pattern of human milk fat is highly dependent on maternal diet, the amounts of constituent fatty acids in human milk are quite variable (Jensen, 1999). Moreover, because medium-chain fatty acids rarely account for more than 10% of the total fatty acid content of human milk, inclusion of up to 50% of total fat as MCTs, as is the case with currently available preterm infant formulas, virtually ensures that the fatty acid pattern of these formulas will not mimic the pattern of human milk. Nevertheless, there is no evidence that the fatty acid patterns of currently available preterm infant formulas, other than perhaps the absence of long-chain polyunsaturated fatty acids (LCPUFAs), are problematic.

Review of the literature

Studies have shown that term infants older than 6 months of age grow normally with a diet providing only approximately 30% of energy as fat (Niinikoski et al., 1997b; Niinikoski et