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April 15, 2011

National List Coordinator
USDA/AMS/NOP, Standards Division
1400 Independence Ave., SW
Room 2646-So., Ag Stop 0268
Washington, DC 20250-0268

Dear Sir or Madam,

Attached with this cover letter is our petition to add the nutrient choline to the National List at §205.605 as a non-agricultural (non-organic) substances allowed in or on processed products labeled as "organic" or "made with organic (specified ingredients).

If you have any questions or require additional information or clarification, please let me know. My contact information is given below.

Sincerely,

Cheryl A. Callen
Director Regulatory Affairs
973-593-7494
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Petition to Include Choline Sources on the National List of Substances Allowed as Ingredients in or on Processed Products Labeled as "organic" or "made with organic (specified ingredients or food group(**s)).”**

Item A:

Section of the National List: § 205.605. Non-agricultural (non-organic) substances allowed in or on processed products labeled as ‘‘organic’’ or ‘‘made with organic (specified ingredients).’’

Specific Listing: "Choline (as the bitartrate or chloride salt)"

Item B:

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

Choline chemically is a positively charged ion. The chemical name of choline is (β-hydroxyethyl) trimethylammonium[1]. When produced in aqueous solution or otherwise dissolved in water, choline forms the compound choline hydroxide. Choline hydroxide is hazardous in case of skin contact (corrosive) or eye contact (corrosive). This substance is not used in food processing.

The specific substances used as choline ingredients for food fortification are the choline salts **choline bitartrate** and **choline chloride**. The chemical name of choline bitartrate is (2-hydroxyethyl) trimethylammonium-L-(+)-tartrate salt. The chemical name of choline chloride is (2-hydroxyethyl) trimethylammonium chloride.

2a. The Petitioner.

Gerber Products Company, 12 Vreeland Road, Florham Park, NJ 07932. Contact: Cheryl A. Callen, Director Regulatory Affairs, Telephone 973-593-7494, Cheryl.Callen@us.nestle.com

2b. Sources of the petitioned substances

Food grade choline bitartrate FCC and choline chloride FCC are standard articles of commerce available from many sources. Recognized sources are as follows:

Choline Bitartrate: Balchem Corp, 52 Sunrise Park Road, New Hampton, NY 10958. Contact Jane Kertesz. Telephone 845-326-5675

Choline Chloride: Mallinckrodt Baker, Inc., 222 Red School Lane, Phillipsburg, NJ 08865. Telephone 800-582-2537

[1] Choline is alternatively designated as (**2**-hydroxyethyl)trimethylammonium.

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3. Current Use.

The specific function of these substances is as "nutrient supplements" [21 CFR 170.3(o)(18)]. These substances are currently used as nonagricultural ingredients to fortify conventional infant and toddler foods and infant and toddlers foods labeled as "organic" with the nutrient choline. Choline addition to infant formulas is permitted or required, depending on the nature of the infant formula, by Federal and International standards for infant formula.

4a. Handling activities for which the substance is used.

Choline salts are added to infant formula products to fortify them to the level of choline provided by breast milk. Infant formulas containing insufficient choline produce fatty liver in animals[2]. Choline salts are added to other infant foods to provide a significant fraction of the Adequate Intake (AI) choline of 150 mg/day established by the Institute of Medicine (see Appendix A).

4b. Mode of action.

In the body, choline is a component of ***acetylcholine*** (the transmitter of cholinergic nerve impulses) as well as brain and nervous tissue lipids. "Choline is a dietary component that is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism."[3] Choline availability modulates brain development in the fetus and infant, and in the adult is important for normal liver and muscle function. It is used to make nerve transmitters, cell membranes and other important chemicals that are essential to the body's functioning.

5. Source of the substances and a detailed description of the manufacturing process.

Choline is produced by the reaction of an aqueous solution of trimethylamine with ethylene oxide at 40°C (104°F) in a closed system. After distilling off and recovering the unreacted trimethylamine, the solution of choline hydroxide is neutralized with an appropriate acid, such as hydrochloric acid or tartaric acid, to form choline chloride or choline bitartrate, respectively. The process was patented in 1956[4] (see Appendix B) and is in the public domain (not CBI). The synthetic solvent isopropyl alcohol ("rubbing alcohol") facilitates production of crystalline choline bitartrate.

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[2] Nutritional adequacy of soy isolate infant formulas in rats: choline. R. C. Theuer and H. P. Sarett. J. Agr. Food Chem. 18, 913-6 (1970).

[3] Choline, Chapter 12, pages 390-422, in "Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Pantothenic Acid, Biotin, and Choline." National Academy Press, Washington, DC. 2000. A synopsis of the information in this chapter, entitled "Choline," S. H. Zeisel and M. A. Caudill. Advances in Nutrition 1, 46-48 (2010), is appended as Appendix A.

[4] U.S. Patent No. 2,774,759. Appended as Appendix B.

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6. Summary of any available previous reviews of the petitioned substance.

Choline addition to infant formula is advised in the Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN[5] Coordinated International Expert Group[6] (Appendix C), which recommends a minimum of 7 mg/100 kilocalories and a maximum of 50 mg/100 kilocalories in infant formula, equivalent to 47 to 335 mg/liter of prepared infant formula. European Commission Directive 2006/141/EC of 22 December 2006 on infant formulae and follow-on formulae and amending Directive 1999/21/EC, the current European regulation for infant formula composition[7] (Appendix C), requires exactly the same minimum and maximum limits for choline in infant formula. EC Directive 2006/1/EC of 22 December 2006 positively lists choline, choline chloride, choline citrate, and choline bitartrate as permitted nutritional substances. Article 27 of the European Commission Regulation (EC) No. 889/2008 of 5 September 2008[8] allows the use of certain products and substances in processing of food labeled as "organic." Section (f) of Article 27 allows minerals (trace elements included), vitamins, amino acids, and micronutrients, but they are authorized only as far their use is legally required in the foodstuffs in which they are incorporated. Since choline is legally required in infant formula in the EC, the EC organic regulations permit choline inclusion in infant formulas labeled as "organic."

As stated above, choline availability modulates brain development in the infant. Because brain development continues for several years after birth, it is important that the infant and young child eating a mixed diet receive an adequate supply of choline. The Institute of Medicine established an Adequate Intake (AI) of choline of 150 mg/day for infants 7 to 12 months of age and an AI of 200 mg/day for children 1 to 3 years of age.

The 1995 TAP review[9] for "nutrient vitamins" cited choline and the choline salts choline chloride and choline bitartrate as "vitamins." The NOSB was provided with this TAP Review prior to their vote on whether to include Nutrient Vitamins on the proposed National List. Consequently, the NOSB in 1995 was made aware that choline was within the scope of substances considered nutrient vitamins when the NOSB voted to add nutrient vitamins to the National List.

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[5] ESPGHAN: European Society for Pediatric Hepatology, Gastroenterology, and Nutrition.

[6] Journal of Pediatric Gastroenterology and Nutrition 41:584–599, November 2005. Authored by the ESPGHAN Committee on Nutrition. Copy appended as part of Appendix C.

[7] Appended as part of Appendix C.

[8] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:250:0001:0084:EN:PDF Article 27 is appended as part of Appendix C.

[9] See 1995 TAP Review, page 7 of 24. Accessed 15 September 2010 at http://www.ams.usda.gov/AMSv1.0/getfile?dDocName=STELPRDC5067006&acct=nopgeninfo

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7. Information regarding the regulatory status of Choline.

Choline is an essential nutrient. A minimum level for choline in infant formula not based on milk has been established by FDA regulation [21 CFR 107.100(a)]. This regulation is consistent with the international Codex Alimentarius Commission Standard for Infant Formula (CODEX STAN 72-1981).

FDA has reviewed the authoritative statement from the Institute of Medicine publication *Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin and Choline.* Based on this review, FDA[10] permits nutrient content claims for choline on the label and in labeling of any qualifying food or dietary supplement product. This nutrient content claim does not apply to food specifically marketed to children under 4 years of age.

The bitartrate and chloride salts of choline are listed as GRAS (generally recognized as safe) by FDA. See Appendix D.

Substance Name	Regulation[11]
Choline (infant formula nutrient specification minimum)	21 CFR 107.100(a)
Choline bitartrate (GRAS)	21 CFR 182.8250
Choline chloride (GRAS)	21 CFR 182.8252

The Food Chemicals Codex monographs for choline chloride and choline bitartrate are attached as Appendix E. The Food Chemicals Codex specification does not allow the use of synthetic (racemic, DL) tartaric acid for the manufacture of choline bitartrate. Only the natural L (+) form of tartaric acid is allowed as a raw material. This is verified by the "Optical (Specific) Rotation" test described in the monograph.

8a. Chemical Abstract Service (CAS) numbers of the substance.

Substance Name	CAS Number	Comment
Choline	62-49-7	
Choline hydroxide	123-41-1	Corrosive to skin and eyes
Choline bitartrate	87-67-2	GRAS, stable crystals
Choline chloride	67-48-1	GRAS, deliquescent/hygroscopic

[10] http://www.fda.gov/Food/LabelingNutrition/LabelClaims/FDAModernizationActFDAMAClaims/ucm073599.htm

[11] FDA Regulations appended as Appendix D.

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8b. Labels of products that contains the petitioned substance.

See Appendix F (Labels).

9. The substances' physical properties and chemical mode of action.

Choline chloride is deliquescent. Choline chloride crystals rapidly absorb moisture from the air, turning the substance into a liquid. This property is a major disadvantage. First of all, water-soluble vitamins such as choline are usually added to infant formulas during manufacture as a dry premix, so this property makes choline chloride unsuitable. Secondly, the absorption of water dilutes the choline concentration, making precise control of the choline addition level very difficult. Finally, the moisture pick-up by choline chloride in a dry premix can reduce the stability of other vitamins. Choline chloride is acceptable for adding to liquid foods and feeds.

Choline bitartrate is a very stable, dry, crystalline substance. Choline is invariably added to powdered infant formulas in the form of choline bitartrate. Choline bitartrate remains dry and does not react with other components of infant formulas or vitamin premixes.

These two GRAS choline salts have very low toxicity. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated choline salts in 1971[12] and established an ADI (Acceptable Daily Intake) of "unlimited," citing "use limited by good manufacturing practice." A report contributed to by NIEHS personnel found that choline actually protects against neuro- and hepatotoxicity caused by the chemical diethanolamine (DEA)[13].

Appendix A summarizes the effects of choline on human health, which contains the conclusion of the Institute of Medicine on the "tolerable upper intake levels" ("UL") of choline by adults (3.5 grams a day). This UL is orders of magnitude greater than the estimated intake from food. The UL for children 1 to 3 years of age is 1 gram a day.

Infant formula is fortified to approximately 160 mg/liter, although some infant formulas contain less than 100 mg/liter. Breast milk contains 160 to 210 mg/liter. The Adequate Intake is 125 mg/day for infants 0 to 6 months of age and 150 mg/day for infants 7 to 12 months of age.

Choline chloride has been widely used as a food additive for animal husbandry since the early 1930s. Choline chloride is used as a dietary source of choline, a lipotropic factor, in poultry[14].

Choline does not persist in the environment. It has a very simple manufacturing procedure in a closed environment, as described above, and excess amounts of reactants are recovered.

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[12] http://apps.who.int/ipsc/database/evaluations/chemical.aspx?chemID=1951 . Copy included in Appendix E.

[13] Final Report on Carcinogens. Background Document for Diethanolamine. March 22, 2002. Prepared for the: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC 27709.

[14] Merck Index, Twelfth Edition, 1996, p. 2261.

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10a. Safety information about the substance including a Material Safety Data Sheet (MSDS).

Material Safety Data Sheets for choline hydroxide (not petitioned), choline chloride and choline bitartrate are attached in Appendix G. The MSDS for choline hydroxide is provided as a comparison to help demonstrate the safety advantages of the two GRAS choline salts that are the subject of this petition.

10b. National Institute of Environmental Health Studies Substance Report.

A specific NIEHS report on choline does not exist, to our knowledge. NIEHS actually has funded university research showing that toxicants can inhibit choline metabolism and extra choline can reverse this adverse effect.[12,15] Persistent environmental toxicants may interfere with nerve transmission by blocking acetylcholine function. Supplements of choline can reverse or prevent this neurotoxicity.

11. Research information about Choline.

Appendix A is a recent synopsis of the authoritative and comprehensive review of the nutritional aspects of choline published by the Institute of Medicine (IOM) in 2000. The IOM review presents a balanced view of the metabolic role of choline and the evidence favoring and opposing the addition of the nutrient choline to the human diet. Its bibliography is extensive.

12. Petition Justification Statement.

The synthetic substances choline chloride and choline bitartrate should be included on the National List at §205.605(b). This will permit the production and sale of infant and toddler foods and infant formula labeled as "organic" to also contain this important nutrient. It will also enable certain infant formulas labeled as "organic" to conform to the nutrient specifications for infant formula required by FDA. Foods for infants and young children labeled as "organic" that are fortified with this nutrient will help ensure an adequate supply of choline during the period of brain development that continues for several years after birth.

In 1998, the Food and Nutrition Board of the Institute of Medicine (IOM) recognized choline as an essential nutrient and set Adequate Intake recommendations. For infants between the ages of 0 to 6 months, the Adequate Intake is 125mg/day; whereas the Adequate Intake for older infants between the ages of 7-12 is 150 mg/day. These estimates are based on the average intake data of infants exclusively fed human milk for the first 6 months of life. All commercially available infant formulas must contain at least 7 mg of choline per 100 kcal[16]. Choline is naturally present in milk based formulas but

[15] Diethanolamine Alters Proliferation and Choline Metabolism in Mouse Neural Precursor Cells. M.D. Niculescu, R. Wu, Z. Guo, K.A. da Costa, and S. H. Zeisel. Toxicol. Sci. (2007) 96 (2): 321-326.

[16] FDA Regulation 21 CFR 107.100.

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additional amounts may be added. Addition is required in non-milk based (soy) formulas. The total amount of choline in human milk does not significantly differ from that found in infant formulas derived from cow's milk and soy-derived infant formulas actually contain more phosphatidylcholine than human or cow's milk[17].

All infant formulas contain choline in amounts varying by manufacturer from 12 mg to 24 mg of choline per 100 kcal (about 5 fl oz). Although these infant formulas meet the nutritional standards set forth by the American Academy of Pediatrics and the regulations set by FDA, a 7-month-old infant consuming between 24 and 32 fl oz of infant formula daily could receive between 58 and 77 mg of choline from his or her infant formula. Unless choline is contributed by complementary foods, the infant fed this formula is likely to consume less than the IOM Adequate Intake level of 150 mg/day.

Because brain development continues for several years after birth, infant and toddler diets should contain adequate levels of choline. Used as part of a varied and healthy diet, foods with added choline can be an appropriate way to assure adequate choline in the infant and toddler diet.

The beneficial effects to human health of the synthetic substance choline are described in Appendix A.

13. Confidential Business Information Statement.

This petition contains no Confidential Business Information.

[17] Holmes-McNary, M.Q., Cheng, W.L., Mar, M.H., Fussell, S, and Zeisel, S.H. Choline and choline esters in human and rat milk and in infant formulas. *Am J Clin Nutr*. 1996; 64:572-576.

Appendices to Choline Petition

Appendix A. Choline, S. H. Zeisel and M. A. Caudill, Advances in Nutrition 1, 46-48 (2010).

Appendix B. U.S. Patent No. 2,774,759. Preparation of choline base and choline salts. Patent issued December 18, 1956.

Appendix C. European recommendation for composition of infant formula.
EC Directive on composition of infant formula.
EC Regulation for organic food: Article 27.

Appendix D. Relevant FDA Regulations:
21 CFR 107.100 Nutrient specifications (for infant formula)
21 CFR 182.8250 Choline bitartrate
21 CFR 182.8252 Choline chloride

Appendix E. Food Chemicals Codex monograph for choline bitartrate.
Food Chemicals Codex monograph for choline chloride
JECFA Evaluation of Choline Salts.

Appendix F. Labels of products that contain the petitioned substance.

Appendix G. Material Safety Data Sheet for choline hydroxide.
Material Safety Data Sheet for choline bitartrate.
Material Safety Data Sheet for choline chloride.

Appendix A. Choline, S. H. Zeisel and M. A. Caudill, Advances in Nutrition 1, 46-48 (2010).

Choline[1,2]

Choline has several important functions. It is a source of methyl groups needed to make the primary methyl donor, *S*-adenosylmethionine; a part of the neurotransmitter acetylcholine; and a component of the predominant phospholipids in membranes (phosphatidylcholine and sphingomyelin) (1). The choline derivative, phosphatidylcholine, is a main constituent of VLDL and is required for VLDL secretion and the export of fat from liver (2). Betaine, formed from choline, is an important osmolyte in the kidney glomerulus and helps with the reabsorption of water from the kidney tubule (3). The choline moiety can be produced endogenously when phosphatidylcholine is formed from phosphatidylethanolamine, mainly in the liver. Despite this capacity to form choline in liver, most men and postmenopausal women need to consume choline in their diets (4); the gene for the enzyme catalyzing this biosynthesis is induced by estrogen (5) and some young nonpregnant women may not need to eat choline (4). Genetic polymorphisms in genes of choline metabolism increase the dietary requirement for choline and almost one-half of young women have a gene polymorphism that makes choline biosynthesis unresponsive to estrogen, making these women's dietary choline requirement similar to men's.

Deficiencies: Healthy humans with normal folate and vitamin B-12 status who were fed a choline-deficient diet developed fatty liver, liver damage [elevated plasma alanine (or aspartate) transaminase] or developed muscle damage (elevated creatine phosphokinase) that resolved when choline was restored to the diet (4,6). Elevations in markers of DNA damage (7) and alterations in lymphocyte gene expression (8) were also observed in choline deficiency. During pregnancy, women in the lowest quartile of dietary choline intake had a higher risk of having a baby with a neural tube defect (NTD)[3] or cleft palate (9,10). In rodent models, maternal dietary choline influences brain development in the fetus (11,12) and increases the prevalence of heart defects (13).

Diet recommendations: In 1998, the U.S. Institute of Medicine's Food and Nutrition Board established an Adequate Intake (AI) and a Tolerable Upper Limit (UL) for choline (14). The AI is 425 and 550 mg/d for women and men, respectively, with more recommended during pregnancy and lactation. The AI for infants is estimated from the calculated intake from human breast milk.

Food sources: Choline and esters of choline are widely distributed in food; however, animal products generally contain more choline per unit weight than plants. Eggs, beef, chicken, fish, and milk as well as select plant foods like cruciferous vegetables and certain beans are particularly good sources of choline providing at least 10% of the daily requirement per serving (15–18). Humans consuming an ad libitum diet ingest between 150 and 600 mg choline/d as free choline and choline esters (10,19–23). In the 2005 NHANES study, only a small portion of Americans in all age groups ate diets that met the recommended intake for choline (24). Foods also contain the choline metabolite betaine (17), which cannot be converted to choline but can be used as a methyl donor, thereby sparing some choline requirements (25,26). Plant-derived foods can be a rich source of betaine (named after beets), with grain products being particularly good sources.

Clinical uses: Hepatic complications associated with total parenteral nutrition (TPN), which include fatty infiltration of the liver and hepatocellular damage, have been reported by many clinical groups. Frequently, TPN must be terminated because of the severity of the associated liver disease. Amino acid-glucose solutions used in TPN of humans contain no choline. The lipid emulsions used to deliver extra calories and essential fatty acids during parenteral nutrition contain choline in the form of phosphatidylcholine (20% emulsion contains 13.2 mmol/L). Some of the liver disease associated with TPN is related to choline deficiency and is prevented with supplemental choline or phosphatidylcholine (27–31). Thus, choline is an essential nutrient during long-term TPN.

Toxicity: The UL for choline was derived from the lowest observed adverse effect level (hypotension) in humans and is 3.5 g/d for an adult (14).

Recent research: Genetic variation likely underlies these differences in dietary requirements for choline. As discussed earlier, several metabolic pathways influence how much choline is required from diet, and single nucleotide polymorphisms in specific genes influence the efficiency of these pathways. Specifically, some polymorphisms in the folate pathways limit the availability of methyltetrahydrofolate and thereby increase the use of choline as a methyl donor, polymorphisms in the *PEMT* gene alter endogenous synthesis of choline, and polymorphisms in other genes of choline metabolism influence dietary requirements by changing the utilization of choline moiety (32,33).

In men, intakes exceeding the choline AI are needed to optimize homocysteine disposal after a methionine load as well as the removal of fat from liver (34). A choline intake exceeding current dietary recommendations was also shown to preserve markers of cellular methylation and attenuate DNA damage in a genetic subgroup of folate-compromised men (35).

Epidemiological studies have linked low dietary choline intake to higher concentrations of proinflammatory markers (36,37) as well as to increased risk of breast cancer (14) and to having a baby with a NTD (7). Elevated NTD risk was also associated with lower concentrations of serum total choline in a folate-fortified population (38). Additionally, genetic variants in choline metabolizing enzymes are associated with excess risk of NTD (39) and altered risk of breast cancer (40).

A recent study in a mouse model of Down Syndrome reported improvements in cognitive function and emotion regulation in

 Adv. Nutr. 1: 46–48, 2010; doi:10.3945/an.110.1010.

Table 1. Dietary Reference Intake values for choline

Population	Age	AI	UL
AI for infants	0–6 mo	125 mg/d, 18 mg/kg	Not possible to establish[1]
	6–12 mo	150 mg/d	
AI for children	1–3 y	200 mg/d	1000 mg/d
	4–8 y	250 mg/d	1000 mg/d
	9–13 y	375 mg/d	2000 mg/d
AI for males	14–18 y	550 mg/d	3000 mg/d
	≥19 y	550 mg/d	3500 mg/d
AI for females	14–18 y	400 mg/d	3000 mg/d
	≥19 y	425 mg/d	3500 mg/d
AI for pregnancy	All ages	450 mg/d	Age-appropriate UL
AI for lactation	All ages	550 mg/d	Age-appropriate UL

[1]Source of intake should be food and formula only. From (14).

mice born to mothers supplemented with choline during the perinatal period (41). This work expands upon earlier work in rodents showing that extra exposure to choline during the perinatal period yielded long lasting beneficial effects on memory, learning and attention (42).

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[2]Author disclosures: S. H. Zeisel has no financial conflict of interest in relation to this manuscript. Dr. Zeisel received grant support from Mead Johnson Nutritionals, Balchem, and the Egg Nutrition Research Center for research studies and serves on an advisory board for Solae, Dupont, Western Almond Board, and Hershey. M. A. Caudill has no financial conflict of interest in relation to this manuscript. Dr. Caudill received grant support from the Egg Nutrition Research Center and from the Beef Checkoff through the National Cattlemen's Beef Association and the Nebraska Beef Council.

[3]Abbreviations used: AI, Adequate Intake; NTD, neural tube defect; TPN, total parenteral nutrition; UL, Tolerable Upper Limit.

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Appendix B. U.S. Patent No. 2,774,759. Preparation of choline base and choline salts. Patent issued December 18, 1956.

United States Patent Office 2,774,759 Patented Dec. 18, 1956

2,774,759

PREPARATION OF CHOLINE BASE AND CHOLINE SALTS

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No Drawing. Application January 6, 1955, Serial No. 480,268

7 Claims. (Cl. 260—251.5)

This invention relates to an improved process of preparing choline base and choline salts and includes choline folate as a new chemical compound.

The use of choline and its salts as therapeutic agents has increased considerably and these agents now occupy an important place both in therapy and as a component along with other vitamins in various dietary supplements. However, because of the nature of choline and its salts it has been difficult to prepare choline and its salts in the high purities necessary when these products are intended for human consumption. Various physical properties and state of matter are also requisite when the products are to be incorporated into pills, capsules and tablets along with other materials. Efficient and economical means of producing choline and its various salts in pure form are, therefore, desirable and necessary.

The customary procedure for the preparation of choline base involves the preparation of choline chloride by any of the conventional procedures, and then treating the choline chloride with silver oxide or silver hydroxide to precipitate silver chloride, leaving the choline base which may then be converted to choline salts by reaction with a suitable acid.

In the described procedure, several steps are involved and the use of costly solvents is required which is an economic disadvantage since anhydrous choline chloride is an expensive starting material.

The present invention is based upon the discovery that when an aqueous solution of trimethylamine is reacted with ethylene oxide, the resulting aqueous solution of choline base can be used directly to prepare various choline salts by neutralization of the choline base with an appropriate acid.

The present invention thereby affords an economic advantage over the standard procedures since not only is an aqueous procedure more economical than the anhydrous choline chloride process, but it is not necessary to go through any steps to isolate the choline base as was necessary heretofore, nor are any costly solvents required since water is the only solvent used.

It has been proposed to prepare tricholine citrate by reacting approximately stoichiometric amounts of ethylene oxide with trimethylamine. In this process, the choline base is generally overneutralized with citric acid because of the presence of some unreacted trimethylamine. The tricholine citrate thus formed is contaminated with trimethylamine citrate which is formed as a consequence of the neutralization of the choline base with citric acid.

In a preferred embodiment of the present invention, we have discovered that by the use of a two-step neutralization procedure in the preparation of various choline salts, such as, for example, trichloline citrate, it is possible to obtain a product which is of a desirably light color and completely uncontaminated with trimethylamine citrate.

In this aspect of the present invention, the aqueous

solution of the choline base, prepared as hereinbefore described, is partially neutralized with, for example, citric acid. The unreacted trimethylamine is then removed by distillation and the remaining choline base is neutralized by adding the required amount of citric acid. The upper limit of neutralization, namely, about 95%, is fairly critical since if somewhat more than 95% neutralization is accomplished, trimethylamine citrate is formed as a side reaction and which remains as a contaminant and which is undesirable when the products are to be used for human consumption. The lower limit of neutralization, however, is somewhat less critical. As a practical matter, not less than about 50% neutralization is ordinarily practical since with more free base present, the greater is the danger of producing a dark colored product. The preferred neutralization is of the order of 85–95%.

In the more general aspects of the present invention, an aqueous solution of the choline base is prepared by reacting approximately stoichiometric amounts of ethylene oxide with an aqueous solution of trimethylamine, keeping the temperature below about 30° C. In practice, there will still be unreacted trimethylamine and which is removed by vacuum distillation, since ethylene oxide is so reactive that various side reactions take place and a 5–15% excess is usually required if the trimethylamine is to be completely reacted. In actual practice, the distillation may be stopped before the evaporation is complete, leaving an aqueous solution of choline base at a convenient concentration of between 10 and 50%. The aqueous solution may then be diluted with water, sufficient to result in a 5–25% solution of the base, and this solution may then be used to prepare the various salts, either by the partial neutralization steps hereinbefore described if the excess trimethylamine has not been completely removed by vacuum distillation, or the various salts may be prepared by a simple neutralization of the choline base with an appropriate acid. The partial neutralization procedure, however, will generally produce a better colored product which is important with liquid preparations. The choline base procedure is usually satisfactory, however, if the product is to be isolated as a solid because most of the dark color washes out in the mother liquor.

While the removal of excess trimethylamine followed by neutralization of the choline base constitutes the preferred procedure and is necessary with liquid preparations, trimethylamine salts of other compounds may be removed by washing when the products are isolated as solids. In this connection, it is interesting to note that choline base is much more stable if the excess trimethylamine is not removed. Choline base without trimethylamine turns dark in a few days while choline base with trimethylamine shows little change in color after several months' storage.

The choline salts may be isolated by conventional means, as by the use of methanol, anhydrous alcohol, etc., or by the use of certain mixed solvents which form the subject matter of the copending application of Whiston and Smith filed concurrently herewith.

Suitable choline salts may be prepared with both organic and inorganic acids. Examples of inorganic acids are hydrochloric acid, nitric acid, phosphoric acid, sulfuric acid, and the like; examples of organic acids which may be used are acetic, propionic, butyric, stearic, and the like; dibasic acids such as oxalic, malonic, succinic, tartaric, citric, gluconic, and the like, as well as amino acids such as glycine, serine, alanine, glutamic, folic, and the like may be used. In general, any type of organic acid may be used if it has sufficient acidity to form a stable choline salt.

In certain instances, especially desirable salts are prepared by this process for certain uses, for example, the folic acid salt of choline. Choline folate, being made up of choline and folic acid, both of which are therapeutic agents, affords a compound useful for combination therapy where the effects of both choline and folic acid are desired. Furthermore, this salt affords a convenient means of incorporating both choline and folic acid into the vitamin formulations since only one compound need be added in place of two.

The invention will be described in greater detail in conjunction with the following specific examples in which the parts are by weight unless otherwise specified.

EXAMPLE 1

Trichline citrate

To 236 parts of a 25% aqueous trimethylamine solution at 30° C. is added 40 parts of ethylene oxide. The mixture is then stirred until the reaction is substantially complete keeping the temperature below about 30° C. The concentration of the choline base in the reaction mixture is then determined potentiometrically and sufficient citric acid is added to neutralize 95% of the choline base present. Unreacted trimethylamine is then removed by distillation at 40–45° C. under a pressure of about 30–50 mm. Sufficient additional citric acid is then added to completely neutralize the choline base, which is present to give tricholine citrate. After treatment with activated charcoal and filtration at 50° C., the tricholine ctirate is isolated by removal of the solvent by distillation under reduced pressure, the solution temperature being kept below 50° C. The tricholine citrate is formed in excellent yield. It has a desirable light color and only traces of trimethylamine.

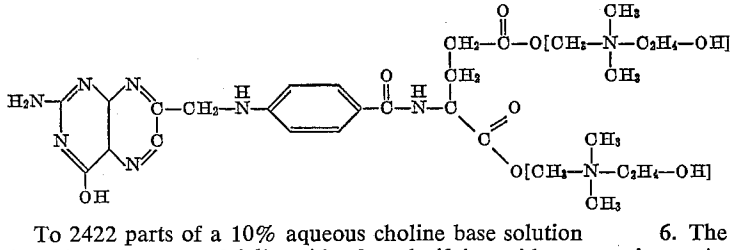
EXAMPLE 2

Choline base

To 236 parts of a 25% aqueous trimethylamine solution at 30° C. is added 40 parts of ethylene oxide. The mixture is then stirred until the reaction is substantially complete, keeping the temperature below about 30° C. Unreacted trimethylamine is removed under vacuum at about 45–55° C., leaving the choline base in a 40–45% aqueous solution. The quality is excellent as only traces of inorganic salts and trimethylamine are present.

EXAMPLE 3

Dicholine folate



To 2422 parts of a 10% aqueous choline base solution is added 441 parts of folic acid; after clarifying with activated charcoal, the water is removed under vacuum resulting in a viscous mass. This is then dissolved in 1530 parts of methanol and the resulting solution is drowned into 10 times its volume of 1,4-dioxane. The choline folate is removed by filtration, washed with acetone and dried at 50–60° C. An almost quantitative yield of crystalline dicholine folate is produced.

EXAMPLE 4

Dicholine mucate

To 2422 parts of a 10% aqueous solution of choline base is added 210 parts of mucic acid. The aqueous solution is clarified by activated charcoal and then evaporated under vacuum to give a viscous mass. This is partially dissolved in 126 parts of methanol. The dicholine mucate is then precipitated by adding an equal volume of isopropanol to the methanolic solution. An excellent yield of dicholine mucate is obtained.

EXAMPLE 5

Mono choline phosphate

To 1211 parts of a 20% aqueous solution of choline base is added 98 parts of phosphoric acid. The aqueous solution is clarified by activated charcoal and concentrated under vacuum to a viscous mass, which is then dissolved in 316 parts of methanol. An equal volume of isopropanol is then added to the methanol solution and the crystalline choline phosphate is then removed by filtration. A good yield of mono choline phosphate (choline dihydrogen phosphate) is obtained. Methanol or anhydrous alcohol may be used for crystallizing the phosphate, but the yields are not as good as with the methanol-isopropanol mixture.

EXAMPLE 6

Choline stearate

To 302.5 parts of a 40% aqueous choline base solution is added 284 parts of stearic acid, dissolved in 276 parts of methanol. After stirring, the solution of choline stearate is given a decolorization treatment with activated charcoal and the clarified solution is then evaporated under vacuum to a slurry. This is poured on to dryer trays and then dried, giving the final stearate with physical characteristics similar to that of a soap.

We claim:

1. In the preparation of a choline salt wherein an aqueous solution of trimethylamine is reacted with ethylene oxide to form choline base, the improvement which comprises first partially neutralizing the aqueous solution of choline base with an acid, distilling off the unreacted trimethylamine under vacuum, and completely neutralizing the remaining choline base.

2. The process according to claim 1 in which the acid is citric acid.

3. The process according to claim 1 in which the acid is folic acid.

4. The process according to claim 1 in which the acid is mucic acid.

5. The process according to claim 1 in which the acid is phosphoric acid.

6. The process according to claim 1 in which the acid is stearic acid.

7. The process according to claim 1 in which the first neutralization is from about 85% to 95%.

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Appendix C. European recommendation for composition of infant formula.

EC Directive on composition of infant formula.

EC Regulation for organic food: Article 27.

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Medical Position Paper

Global Standard for the Composition of Infant Formula: Recommendations of an ESPGHAN Coordinated International Expert Group

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ABSTRACT
The Codex Alimentarius Commission of the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) develops food standards, guidelines and related texts for protecting consumer health and ensuring fair trade practices globally. The major part of the world's population lives in more than 160 countries that are members of the Codex Alimentarius. The Codex Standard on Infant Formula was adopted in 1981 based on scientific knowledge available in the 1970s and is currently being revised. As part of this process, the Codex Committee on Nutrition and Foods for Special Dietary Uses asked the ESPGHAN Committee on Nutrition to initiate a consultation process with the international scientific community to provide a proposal on nutrient levels in infant formulae, based on scientific analysis and taking into account existing scientific reports on the subject. ESPGHAN accepted the request and, in collaboration with its sister societies in the Federation of International Societies on Pediatric Gastroenterology, Hepatology and Nutrition, invited highly qualified experts in the area of infant nutrition to form an International Expert Group (IEG) to review the issues raised. The group arrived at recommendations on the compositional requirements for a global infant formula standard which are reported here. ***JPGN 41:584–599, 2005.*** **Key Words:** Bottle feeding—Food standards—Infant food—Infant formula—Infant nutrition—Nutritional requirements. © 2005 Lippincott Williams & Wilkins

BACKGROUND OF THE ESPGHAN COORDINATED INTERNATIONAL EXPERT GROUP CONSULTATION

The Codex Alimentarius Commission was created in 1963 by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) to develop food standards, guidelines and related texts such as codes of practice under

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the Joint FAO/WHO Food Standards Program (www.codexalimentarius.net). The main purposes of this program are protecting the health of consumers and ensuring fair trade practices in the food trade, and promoting coordination of all food standards work undertaken by international governmental and nongovernmental organizations. The major part of the world's population lives in more than 160 countries that are members of the Codex Alimentarius. The Codex Alimentarius has developed a large number of standards in the area of food quality and safety, which are of paramount importance for the protection of public health and fair trade on all continents.

Codex Standard 72 on Infant Formula (1) was adopted in 1981 and is based on scientific knowledge as available in the 1970s. In view of the progress in the scientific understanding of nutritional needs of infants and in the methods of formula production, the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed to develop a revision of this standard with a part A defining the requirements of infant formulae (intended to meet the normal nutritional requirements of infants) and a part B defining the requirements of foods for special medical purposes for infants (FSMP; intended for infant patients with special dietary needs due to diseases). An Electronic Working Group (EWG) was charged to seek agreement on the essential composition of infant formula, but due to time constraints and other factors could not finish its task.

Therefore, CCNFSDU decided in November 2004 to request additional advice from an international group of scientific experts in the area of infant nutrition. CCNFSDU asked the Committee on Nutrition of ESPGHAN (The European Society for Pediatric Gastroenterology, Hepatology and Nutrition), which is a member of the EWG, to coordinate this exercise. ESPGHAN was asked to initiate a consultation process with the international scientific community to provide proposals on nutrient levels in infant formulae, based on scientific analysis and taking into account existing scientific reports on the subject. It was requested that the scientific advice for possible solutions should be provided in a clearly stated, transparent and comprehensible manner. This paper is expected by CCNFSDU to facilitate the process of decision taking at the following 27th session of this Codex Committee in November 2005.

ESPGHAN accepted the request and, in collaboration with its sister societies in the global Federation of International Societies on Pediatric Gastroenterology, Hepatology and Nutrition (FISPGHAN), invited highly qualified experts in the area of infant nutrition to form an International Expert Group (IEG) to review the issues raised. Criteria for participation in the IEG included expertise in pediatric nutrition research and active contributions to international scientific societies or advisory bodies dealing with pediatric nutrition issues. In order to ensure that experts were in a position to provide objective and disinterested scientific advice, all participating experts submitted a written declaration of personal and nonpersonal (institutional) interests. These were reviewed and approved both by the chair of the IEG (BK) and the chair of the CCNFSDU EWG (HP) as a prerequisite for accepting the participation of the respective experts.

The IEG members were provided with background material, including a summary of the status of the CCNFSDU draft standard on infant formula provided by the EWG chair in January 2005. The IEG members reviewed the proposals taking into account the available scientific evidence, including the recent reviews performed by the Life Science Research Office (LSRO) of the American Societies of Nutritional Sciences (2) and the Scientific Committee on Food of the European Commission (SCF) (3). IEG members submitted written comments, and a meeting was held from 26–29 April 2005 at Tutzing (near Munich), Germany to thoroughly discuss all issues. At this meeting, unanimous agreement was reached on each compositional recommendation made in this report. However, after the meeting one IEG member raised concerns with respect to the recommended minimum iron level, because of a recommendation for a higher minimum iron level by the national academy of pediatrics in the member's country, and withdrew the support for this value. All other IEG members maintained their decision in favor of this recommendation. This final report was written, circulated to all IEG members, approved and submitted to the CCNFSDU and its EWG in June 2005.

GENERAL CONSIDERATIONS

The IEG discussed some general considerations as the basis of its deliberations. The IEG recognizes the multiple benefits of breast feeding for child health (4) and strongly supports breast feeding as the ideal form of infant feeding which should be actively promoted, protected and supported. Infant formulae are intended to serve as a substitute for breast milk in infants who cannot be fed at the breast, or should not receive breast milk, or for whom breast milk is not available (5). The composition of infant formulae should serve to meet the particular nutritional requirements and to promote normal growth and development of the infants for whom they are intended.

Data on the composition of human milk of healthy, well-nourished women can provide some guidance for the composition of infant formulae, but gross compositional similarity is not an adequate determinant or indicator of the safety and nutritional adequacy of infant formulae. Human milk composition shows remarkable variation. Moreover, there are considerable differences in the bioavailability and metabolic effects of similar contents of many specific nutrients in human milk and formula, respectively. Therefore, the adequacy of infant formula composition should be determined by a comparison of

its effects on physiological (e.g. growth patterns), biochemical (e.g. plasma markers) and functional (e.g. immune responses) outcomes in infants fed formulae with those found in populations of healthy, exclusively breast-fed infants.

The IEG concludes that infant formulae should only contain components in such amounts that serve a nutritional purpose or provide another benefit. The inclusion of unnecessary components, or unnecessary amounts of components, may put a burden on metabolic and other physiologic functions of the infant. Those components taken in the diet, which are not utilized or stored by the body, have to be excreted, often as solutes in the urine. Since water available to form urine is limited and the infant's ability to concentrate urine is not fully developed during the first months of life, the need to excrete any additional solutes will reduce the margin of safety, especially under conditions of stress, such as fever, diarrhea or during weight loss.

Minimum and maximum values of nutrient contents in infant formulae are suggested with the goal to provide safe and nutritionally adequate infant formula products that meet the nutritional requirements of healthy babies. The IEG considered that such minimum and maximum values should be based, where available, on adequate scientific data on infant requirements and the absence of adverse effects. In the absence of an adequate scientific evaluation, minimum and maximum values should at least be based on an established history of apparently safe use. The establishment of minimum and maximum values also should take into account, where possible, other factors such as bioavailability and losses during processing and shelf life. Minimum and maximum values refer to total nutrient contents of infant formulae as prepared ready for consumption according to the instructions of the manufacturer.

While the IEG bases its conclusions on a considered review of the evidence available at this time, it recognizes that future scientific progress will necessitate revisiting and updating the compositional standards for infant formulae. The IEG considers it an obligation for Codex Alimentarius to review, on a regular basis, the adequacy of its compositional standards for infant foods.

The IEG recommends that the addition of new ingredients to infant formulae, or of established ingredients in newly determined amounts beyond the existing standards on formula composition, should be made possible if the safety, benefits and suitability for nutritional use by infants have been established by generally accepted scientific data. Given the accumulating evidence that the composition of the diet of infants has a major impact on short and long term child health and development, the IEG finds it imperative that the scientific evidence to support modifications of infant formulae beyond the established standards must always be overseen and evaluated by independent scientific bodies before the acceptance of the introduction of such products to the market.

RECOMMENDATIONS FOR INFANT FORMULA COMPOSITION

Infant formula is a product based on milk of cows or other animals and/or other ingredients which have been proven to be suitable for infant feeding. The nutritional safety and adequacy of infant formula should be scientifically demonstrated to support normal growth and development of infants.

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, and it shall contain per 100 kcal the nutrients, with minimum and maximum levels where applicable, as listed in Table 1.

In addition to the compositional requirements listed in Table 1, other ingredients may be added 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 (Table 2). The IEG takes the view that the mere presence of a substance in human milk by itself does not justify its addition to formula, but that a benefit of the addition should be shown.

The suitability for the particular nutritional uses of infants and the safety of additional compounds added at the chosen levels shall be scientifically demonstrated. The formula shall contain sufficient amounts of these substances that have been demonstrated to achieve the intended effect. The IEG concludes that only limited orientation can be deducted from levels of components in human milk in view of possible differences in bioavailability and the fact that substances other than components found in human milk may need to be used to achieve the desired effects in infants.

COMMENTS

The available scientific information on infant nutrient needs and evaluation of infant formula composition has recently been reviewed (2,3). Therefore, no attempt is made to review here the totality of the available information; rather, our comments focus on issues where different views have arisen in the past.

Proteins from the milk of animals other than cows or from various plant sources are considered potentially suitable for use in infant formulae. However, the suitability and safety should be adequately evaluated and documented for each protein source to be used. At this time the IEG does not recommend to refer to specific animal protein sources other than cows' milk in the text of the standard. As of today, most of the evidence published in the international literature that includes conclusive studies in human infants is limited to the evaluation of cows' milk or soy protein based infant formulae.

TABLE 1. *Proposed compositional requirements of infant formula*

Component	Unit	Minimum	Maximum
Energy	kcal/100 ml	60	70
Proteins			
Cows' milk protein	g/100 kcal	1.8*	3
Soy protein isolates	g/100 kcal	2.25	3
Hydrolyzed cows' milk protein	g/100 kcal	1.8†	3
Lipids			
Total fat	g/100 kcal	4.4	6.0
Linoleic acid	g/100 kcal	0.3	1.2
α-linolenic acid	mg/100 kcal	50	NS
Ratio linoleic/α-linolenic acids		5:1	15:1
Lauric + myristic acids	% of fat	NS	20
Trans fatty acids	% of fat	NS	3
Erucic acid	% of fat	NS	1
Carbohydrates			
Total carbohydrates‡	g/100 kcal	9.0	14.0
Vitamins			
Vitamin A	μg RE/100 kcal§	60	180
Vitamin D_3	μg/100 kcal	1	2.5
Vitamin E	mg α-TE/100 kcal‖	0.5¶	5
Vitamin K	μg/100 kcal	4	25
Thiamin	μg/100 kcal	60	300
Riboflavin	μg/100 kcal	80	400
Niacin#	μg/100 kcal	300	1500
Vitamin B_6	μg/100 kcal	35	175
Vitamin B_{12}	μg/100 kcal	0.1	0.5
Pantothenic acid	μg/100 kcal	400	2000
Folic acid	μg/100 kcal	10	50
Vitamin C	mg/100 kcal	8	30
Biotin	μg/100 kcal	1.5	7.5
Minerals and trace elements			
Iron (formula based on cows' milk protein and protein hydrolysate)	mg/100 kcal	0.3**	1.3
Iron (formula based on soy protein isolate)	mg/100 kcal	0.45	2.0
Calcium	mg/100 kcal	50	140
Phosphorus (formula based on cows' milk protein and protein hydrolysate)	mg/100 kcal	25	90
Phosphorus (formula based on soy protein isolate)	mg/100 kcal	30	100
Ratio calcium/phosphorus	mg/mg	1:1	2:1
Magnesium	mg/100 kcal	5	15
Sodium	mg/100 kcal	20	60
Chloride	mg/100 kcal	50	160
Potassium	mg/100 kcal	60	160
Manganese	μg/100 kcal	1	50
Fluoride	μg/100 kcal	NS	60
Iodine	μg/100 kcal	10	50
Selenium	μg/100 kcal	1	9
Copper	μg/100 kcal	35	80
Zinc	mg/100 kcal	0.5	1.5
Other substances			
Choline	mg/100 kcal	7	50
Myo-inositol	mg/100 kcal	4	40
L-carnitine	mg/100 kcal	1.2	NS

*The determination of the protein content of formulae based on non-hydrolyzed cows' milk protein with a protein content between 1.8 and 2.0 g/100 kcal should be based on measurement of true protein ([total N minus NPN] × 6.25) (31).

†Formula based on hydrolyzed milk protein with a protein content less than 2.25 g/100 kcal should be clinically tested.

‡Sucrose (saccharose) and fructose should not be added to infant formula.

§1 μg RE (retinol equivalent) = 1 μg all-trans retinol = 3.33 IU vitamin A. 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.

‖1 mg α-TE (α-tocopherol equivalent) = 1 mg d-α-tocopherol.

¶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 α-TE/g linoleic acid (18:2n-6); 0.75 mg α-TE/g α-linolenic acid (18:3n-3); 1.0 mg α-TE/g arachidonic acid (20:4n-6); 1.25 mg α-TE/g eicosapentaenoic acid (20:5n-3); 1.5 mg α-TE/g docosahexaenoic acid (22:6n-3).

#Niacin refers to preformed niacin.

**In populations where infants are at risk of iron deficiency, iron contents higher than the minimum level of 0.3 mg/100 kcal may be appropriate and recommended at a national level.

NS, not specified.

TABLE 2. *Proposed levels of optional ingredients, if added*

Optional ingredients	Unit	Minimum	Maximum
Taurine	mg/100 kcal	0	12
Total added nucleotides	mg/100 kcal	0	5
Cytidine 5′-monophosphate (CMP)	mg/100 kcal	0	1.75
Uridine 5′-monophosphate (UMP)	mg/100 kcal	0	1.5
Adenosine 5′-monophosphate (AMP)	mg/100 kcal	0	1.5
Guanosine 5′-monophosphate (GMP)	mg/100 kcal	0	0.5
Inosine 5′-monophosphate (IMP)	mg/100 kcal	0	1.00
Phospholipids	mg/100 kcal	0	300
Docosahexaenoic acid*	% of fat	0	0.5

*If docosahexaenoic acid (22:6n-3) is added to infant formula, arachidonic acid (20:4n-6) contents should reach at least the same concentration as DHA. The content of eicosapentaenoic acid (20:5n-3) should not exceed the content of docosahexaenoic acid.

The IEG discussed whether one should always provide a label declaration on energy density per unit of powder, or of nutrient content per g powder or per unit of formula as ready for consumption. While it was appreciated that national authorities may choose to request additional label information, no necessity was seen to introduce a general requirement. In this report nutrient contents of infant formulae are generally given per unit of energy (here per 100 kcal), which is physiologically meaningful.

Energy Density

Studies with current methodology have revealed an average energy density of human milk of about 650 kcal/L (6,7), which is some 5–10% less than previously assumed (8). Also, total energy expenditure of infants was found to be lower than previously assumed. A milk energy density markedly higher than typically found in human milk may increase total energy intake and lead to a higher than desirable weight gain. A high weight gain in healthy infants has been associated with an increased risk of later obesity (9,10). The IEG proposes an energy density of infant formulae in the range of 60–70 kcal/100 ml, which is appropriate to support physiological rates of weight gain in healthy infants.

Proteins

Sources of Proteins

Minimum and maximum values are provided for cows' milk proteins, soy protein isolates, and hydrolyzed cows' milk proteins because published data are available for these protein sources that allow the delineation of such minimum and maximum values (2,3). The suitability for use in infant formulae of other proteins sources and their adequate minimum and maximum amounts should be documented on a case-by-case basis. With the information available to the IEG from the published and internationally accessible scientific literature, no recommendations can be made at this time for minimum and maximum amounts of other protein sources.

Nitrogen Conversion Factor

The definition of minimum and maximum values for protein contents requires a prior agreement on the method of calculation of protein, which is usually based on a measurement of nitrogen content multiplied by a conversion factor. Different food proteins contain differing amounts of nitrogen, however, FAO/WHO use a factor of 6.25 for all their reports on protein requirement and quality, based on a 16% (by weight) nitrogen content of mixed protein. For unmodified cows' milk protein a nitrogen conversion factor of 6.38 (i.e. 15.7% nitrogen by weight of total protein) has been determined in the 19th century (11) and is widely used in Codex Standards on milk proteins, both whey and casein, until today. The IEG has no objection to the use of a nitrogen conversion factor of 6.38 for unmodified cows' milk protein and whole cows' milk in general food products, but it also has no objection to the default use of a nitrogen conversion factor of 6.25 in the Codex Alimentarius Guidelines on Nutrition Labeling (12). However, when considering the choice of a nitrogen conversion factor for infant formula protein it is important to appreciate the rather different nitrogen conversion factors of various proteins and protein fractions in bovine milk (Table 3) (13).

Proteins derived from cows' milk used in current infant formulae are usually modified, e.g. enriched in whey protein fractions and other nitrogen containing components with lower N conversion factors than caseins

TABLE 3. *Milk contents and nitrogen conversion factors for isolated bovine milk proteins (without carbohydrate), and for protein fractions**

Bovine milk proteins and protein fractions	Content in milk (g/L)	N conversion factor
α_{s1}-Casein	10.0	6.36
α_{s2}-Casein	2.6	6.29
β-Casein	9.3	6.37
κ-Casein	3.3	6.12
γ-Casein	0.8	6.34
α-Lactalbumin	1.2	6.25
Bovine serum albumin	0.4	6.07
Immunoglobulin	0.8	6.00
Proteose-peptone 5, 8F, 8S	0.5	6.54
Proteose-peptone 3	0.3	5.89
Lactoferrin	0.1	5.88
Milk fat globule membrane	0.4	6.60
Whole milk	33.0	6.31
Acid casein		6.33
Paracasein		6.31
Acid whey		6.21
Rennet whey		6.28

*Adapted from 71.

(Table 3). Variations of nonprotein nitrogen (NPN) contents in infant formulae depending on the methods of production result in further marked changes of the nitrogen conversion factor. Therefore, the use of a nitrogen conversion factor of 6.38 for all milk derived protein sources in infant formulae is not justified. While it would be theoretically conceivable that an individual nitrogen conversion factor might be determined for each product, based on an analysis of its contents of total nitrogen, amino acids and nonprotein nitrogen, this is not feasible in practice. Therefore, it is recommended to use the following calculation for all types of infant formula:

protein content of infant formulae (g) = nitrogen (g) × 6.25

It is emphasized here that the recommendations made by the IEG on formula protein contents are based on this nitrogen conversion factor and cannot be used without adaptation if other nitrogen conversion factors are applied.

Nonprotein Nitrogen

It has been proposed that a maximum level of nonprotein nitrogen (NPN) contents in infant formulae should be set (3), because the proportional content of metabolizable amino acids is usually expected to decrease with a higher percentage of total nitrogen comprised by NPN. In human milk some 20–25% of total nitrogen is contributed by nonprotein nitrogen (NPN), of which up to 50% may be metabolically used (14,15). NPN contents in infant formulae, which tend to be used to a lesser extent by the recipient infants, may account for up to 20% of total nitrogen in formulae based on nonhydrolyzed cows' milk proteins, while relatively high NPN contents may be found in some whey fractions separated by ion-exchange, electrodialysis or ultrafiltration, and up to 25% or more in infant formulae based on soy protein isolates that are partially hydrolyzed for technological reasons, or in infant formulae based on cows' milk protein hydrolysates (2,3,16,17). The IEG discussed this question extensively and acknowledges that the definition of protein quality by a maximum content of NPN has some limitations. For example, the addition of some whey based fractions and other nitrogen containing compounds may increase the biologic value of the formula along with increasing NPN content. Furthermore, the same maximum value for NPN content cannot be applied to formulae based on intact milk proteins as well as formulae based on hydrolyzed milk proteins or soy protein isolates, because the latter two types of formulae contain a larger portion of nitrogen as NPN. The IEG also concluded that the setting of a minimal amount of total nitrogen and of dietary indispensable amino acids (cf. Table 4), along with the general requirement that infant formula should serve to promote normal infant growth and development, would generally suffice to assure an adequate nitrogen intake. Therefore, the IEG concludes that there is no general necessity to limit the maximum NPN content in infant formulae, provided that the other requirements recommended in this report are fulfilled.

TABLE 4. *Proposed values for amino acid contents in the human milk reference protein expressed as g/100 g protein and as mg/100 kcal*

Amino acid	g/100 g protein	mg/100 kcal
Cystine	2.1	38
Histidine	2.3	41
Isoleucine	5.1	92
Leucine	9.4	169
Lysine	6.3	114
Methionine	1.4	24
Phenylalanine	4.5	81
Threonine	4.3	77
Tryptophan	1.8	33
Tyrosine	4.2	75
Valine	4.9	99

Infant formula should contain per 100 kcal an available quantity of each of the amino acids listed at least equal to that contained in the reference protein, as shown in this table. For calculation purposes, the concentrations of phenylalanine and tyrosine may be added together if the phenylalanine to tyrosine ratio is in the range of 0.7–1.5 to 1, and the concentrations of methionine and cysteine may be added together if the methionine to cysteine ratio is in the range of 0.7–1.5 to 1.

Amino Acid Contents of Human Milk Protein and Requirements for Amino Acid Contents of Formula Protein

The principal nutritional function of food protein is to meet physiological needs by supplying adequate amounts of dietary indispensable (essential) and of dietary conditionally indispensable (conditionally essential) amino acids, and of total nitrogen. In agreement with LSRO and SCF (2,3), the IEG recommends that evaluation of formula protein composition should use an amino acid score based on human milk protein composition as the reference.

The mean amino acid contents in human milk have been calculated by the LSRO report based on analyses published in the 1980s and 1990s (18–21). However, one of these publications is on transitional milk (21), and only one has analyzed complete 24-hour collections of human milk (18). The Food and Nutrition Board of the Institute of Medicine (22) proposed a modified amino acid pattern of human milk, based on 4 references (18,23–25). The reference unit in the different sources is not the same although expressed as mg amino acid per g protein. For example ''protein'' is the sum of total anhydrous amino acids (18,24) or total nitrogen multiplied by 6.38 (23) or total nitrogen minus NPN multiplied by an unknown factor (25). To avoid this problem it seems advisable to refer the individual amino acid content to the nitrogen content to avoid confusion about the nature of the protein calculation, as suggested by the

SCF (3). The IEG has calculated mean values based on published studies on the amino acid content of human milk, taking into account reports with measurements of the total nitrogen content and/or the calculation method for the protein content, including a reference on a large number of human milk samples published in the Japanese language (26) which had not been considered in the previous reports of LSRO and SCF (2,3) (Table 5). These values are also expressed as content of amino acids in mg/g protein (total nitrogen × 6.25) and as mg amino acids/100 kcal, based on a minimum protein content of 1.8 g/100 kcal (Table 4). These calculated values are very similar to those previously suggested by LSRO and SCF.

Infant formula should contain per 100 kcal an available quantity of the amino acids listed in Table 4 in amounts at least equal to those contained in the reference protein. For calculation purposes, the concentrations of phenylalanine and tyrosine, and of methionine and cysteine, respectively, may be added together if the phenylalanine to tyrosine ratio or the methionine to cysteine ratio, respectively, is in the range of 0.7–1.5:1, which is the usual range of these ratios in both human milk and body protein (27–29). The IEG sees no necessity to set maximum levels of individual amino acid contents in infant formulae if the maximum levels of protein are set as recommended.

Protein Content in Infant Formulae Based on Cows' Milk Protein

The available data suggest that a crude protein content of 1.8 g/100 kcal in infant formula, while higher than the protein supply with breast milk, may be marginal for normal growth in young infants, and thus the amount of amino acids supplied to the infant at such low levels of nitrogen intake appears to be critical (2,3). Therefore, it is recommended that protein contents of formulae with a crude protein content (30) between 1.8 and 2.0 g/100 kcal should be based on measurement of true protein ([total N minus NPN] × 6.25) (31), to guarantee a minimum amount of amino acid nitrogen available for protein synthesis. Protein content of infant formula should not exceed 3 g/100 kcal.

Protein Contents in Infant Formulae Based on Hydrolyzed Cows' Milk Proteins

A variety of different cows' milk protein hydrolysates have been used in infant formulae, which may differ in total content, relative composition and bioavailability of amino acids. While the term ''partial'' has sometimes been used to characterize a less extensive degree of protein hydrolyzation, there are no agreed criteria to strictly define a ''partial hydrolysate''; therefore, the use of this term is not supported. Major differences have been reported for different protein hydrolysate formulae with respect to nitrogen retention and growth in the recipient infants (32,33), which point to a potentially significant variation in the biologic value of different hydrolysates. For optimal utilization the hydrolyzed protein source should have a pattern of indispensable amino comparable to that shown in Table 5. The IEG recommends that infant formulae based on cows' milk protein

TABLE 5. *Amino acid content of human milk from published studies which report measurements of the total nitrogen content and/or the calculation method for the protein content, expressed as mg per gram nitrogen*

	Authors								
	Lönnerdal & Forsum (1985) (72)	Darragh & Moughan (1998) (23)	Bindels & Harzer (1985) (73)	Janas et al. (1987) (19)	Villalpando et al. (1998) (25)		Räihä et al. (2002) mod. Nayman et al. (1979) (74)	Yonekubo et al. (1991) (26)	
					24 hours, pooled @ 4–6 months				
Samples	Pooled bank milk @ 4–16 weeks	Pooled over 20 days @ 10–14 weeks (n = 20)	24 hours, pooled @ 5 weeks (n = 10)	24 h pooled @ 8 weeks (n = 10)	Mexico 40	Houston 40	Pooled bank milk @ >1 month	Milk @ 21 days–2 months	**Mean amino acid content (mg/g nitrogen)**
Arginine	157	200	281	184	168	184	172	223	**196**
Cystine (half)	111	173	108	101	167	134	133	118	**131**
Histidine	111	156	255	112	112	108	122	150	**141**
Isoleucine	242	333	376	306	292	331	300	374	**319**
Leucine	457	598	713	611	528	541	572	667	**586**
Lysine	314	406	522	365	366	408	361	421	**395**
Methionine	78	90	89	73	99	76	83	92	**85**
Phenylalanine	153	243	344	183	440	439	217	240	**282**
Threonine	217	316	344	251	248	242	256	269	**268**
Tryptophan	NA	NA	172	79	112	89	111	122	**114**
Tyrosine	201	241	369	191	292	299	233	249	**259**
Valine	253	327	376	267	286	331	317	364	**315**

NA, not analyzed.

hydrolysates with a content of protein hydrolysate less than 2.25 g/100 kcal should be clinically tested, and such products should only be accepted if the results have been evaluated by an independent scientific body before introduction into the market. The protein content of infant formulae based on cows' milk protein hydrolysates should not be less than 1.8 g/100 kcal and not be greater than 3.0 g/100 kcal.

Protein Contents in Infant Formulae Based on Soy Protein Isolates

A higher minimum protein level is recommended for infant formulae with intact proteins other than intact cows' milk protein, to correct for potentially lesser digestibility and biologic value of the nitrogen content, considering that there is a paucity of data documenting adequacy. Formulae based on soy protein isolates should have a minimum protein content of 2.25 g/100 kcal and a maximum protein content of 3.0 g/100 kcal.

Lipids

Total Fat

The recommended total fat content of 4.4–6.0 g/100 kcal is equivalent to about 40–54% of energy content which is similar to values found typically in human milk (34).

Essential Fatty Acids

A linoleic acid (18:2n-6) content of 300 mg/100 kcal (about 2.7% of energy intake) suffices to cover the minimum linoleic acid requirement. A maximum value for linoleic acid content of 1200 mg/100 kcal is considered necessary because high intakes may induce untoward metabolic effects with respect to lipoprotein metabolism, immune function, eicosanoid balance and oxidative stress.

The omega-3 fatty acid α-linolenic acid (18:3n-3) is considered a dietary indispensable fatty acid and serves as a precursor for the synthesis of docosahexaenoic acid (22:6n-3), whose availability has been related to infant development. However, under certain circumstances high intakes of α-linolenic acid may increase the risk of lipid peroxidation, product rancification, and may adversely affect formula stability. Given the limited knowledge on the activity of in vivo formation of docosahexaenoic acid from the precursor α-linolenic acid and on α-linolenic acid requirements in infancy, a minimum α-linolenic acid (18:3n-3) content of 50 mg/100 kcal (about 0.45% of energy intake) is recommended.

To ascertain a proper balance between linoleic and α-linolenic acids as well as the long-chain polyunsaturated fatty acids (LC-PUFA) and eicosanoids resulting from their metabolism, a linoleic/α-linolenic acid ratio in the range of 5–15 to 1 is recommended. The implementation of this ratio also results in an appropriate limitation of the α-linolenic acid contents to no more than 1/5 of 1200 mg/100 kcal, i.e. 240 mg/100 kcal. Therefore, no further maximum level of α-linolenic acid needs to be set.

Lauric and Myristic Acids

In consideration of the potential negative effects of lauric acid and myristic acid on serum cholesterol and lipoprotein concentrations, the sum of myristic acid and lauric acid should not exceed 20% of total fat contents.

Trans Fatty Acids

Trans fatty acids have no known nutritional benefit for infants, but a number of untoward biologic effects have been attributed to trans fatty acid consumption, such as impairment of microsomal desaturation and chain elongation of essential fatty acids, alterations of lipoprotein metabolism and potential impairment of early growth (35–37). Therefore, prudence dictates the limitation of these substances in infant formulae (2). Considering that the concentration of trans fatty acids in bovine milk fat varies, that formulae may contain as much as 40–50% of the fat as bovine milk fat, and also taking the view that the use of hydrogenated oils in infant and follow-on formulae should be discouraged, the IEG recommends that the contents of trans fatty acids should not exceed 3% of total fat content.

Erucic Acid

While erucic acid has no known nutritional benefit for infants, observations in animals have indicated potential myocardial alterations. The IEG recommends that erucic acid contents acids should not exceed 1% of total fat content.

Carbohydrates

Total Carbohydrates

Carbohydrates are an essential source of energy for the infant. Taking into account the glucose needs of the human brain, the recommended minimum total carbohydrate content of 9.0 g/100 kcal is based on a calculation of glucose needs for obligatory central nervous system oxidation while minimizing the contribution of gluconeogenesis (2,3). The IEG proposes a maximum carbohydrate content of 14.0 g/100 kcal being equivalent to about 56% of energy content.

Lactose

The dominant digestible carbohydrate in human milk is lactose, which provides about 40% of the energy value. Lactose is considered to provide beneficial effects for

gut physiology, including prebiotic effects, softening of stools, and enhancement of water, sodium and calcium absorption. Therefore, the IEG considers it prudent to include lactose in infant formula. However, a specific need of young infants for lactose has not been demonstrated. The possible beneficial effects of lactose on gut physiology, gut microflora, stool consistency, and the absorption of water, sodium and calcium by passive nonsaturable diffusion are not restricted to lactose, but may at least in part be achieved by other components in infant formula. Therefore, no minimum or maximum levels can be set based on available scientific evidence.

Glucose

Glucose is found only in minor amounts in human milk and is considered unsuitable for routine use in infant formula. During heat treatment of formula, glucose may react nonenzymatically with protein and form Maillard products (2). The addition of glucose to infant formula would also lead to a marked increase of osmolality, which is not desirable and may cause untoward effects in the recipient infants; the addition of 1 g glucose per 100 ml formula increases osmolality by 58 mOsm/kg. Therefore, the addition of glucose to infant formulae is not recommended.

Sucrose (saccharose) and Fructose

Feeding of formulae with added fructose or sucrose, a disaccharide containing glucose and fructose, may lead to severe adverse effects including death in young infants affected by hereditary fructose intolerance. Hereditary fructose intolerance (aldolase B or fructose-1-phosphate aldolase deficiency) is a potentially fatal disease with a reported incidence as high as 1:20,000 in some populations. Affected young infants fed fructose or saccharose containing formulae develop hypoglycemia, vomiting, malnutrition, liver cirrhosis and particularly at a young age also sudden death. Given the severe adverse effects of dietary fructose supply in early infancy, the IEG recommends that sucrose and fructose should not be added to infant formulae intended for feeding during the first 4–6 months of life.

Starches

Considering the ability of infants to digest starches and the possible need to include some starch contents in infant formulae for technological reasons, the IEG supports that starches (precooked or gelatinized) may be added to infant formulas up to 30% of total carbohydrates or up to 2 g/100 ml.

Vitamins

Lipid Soluble Vitamins

The lipid-soluble vitamins A, E, D and K are deposited in body fats, such as adipose tissue. High intakes over prolonged periods of time may thus lead to their tissue accumulation and may induce untoward effects. Therefore, both too low and too high intakes should be avoided.

Vitamin A

Considering vitamin A contents in human milk, a presumed higher bioavailability from human milk than infant formula, reference intake values and upper tolerable intake levels, a content of 60–180 μg RE/100 kcal (retinol equivalent, 1 μg RE = 3.33 IU vitamin A = 1 μg all-*trans* retinol) is recommended. Since the relative equivalence of β-carotene and retinol in infants is not known and previously assumed equivalence factors may not be adequate, vitamin A contents in infant formulae should be provided by retinol or retinyl esters, while any contents of carotenoids should not be included in the calculation and declaration of vitamin A activity.

Vitamin D

No conclusive evidence is available to allow a comparative assessment of the biologic activity of dietary vitamin D_3 and vitamin D_2 in infants. Therefore, it is recommended to continue to use vitamin D_3 in infant formulae, rather than vitamin D_2, until such comparative data might become available. In agreement with the considerations discussed by previous expert panels (2,3), a vitamin D_3 content in the range of 1–2.5 μg/100 kcal is recommended.

Vitamin E

Infant formula should contain 0.5–5 mg α-TE/100 kcal (α-tocopherol equivalent, 1 mg α-TE = 1 mg d-α-tocopherol), but not less than 0.5 mg/g linoleic acid or equivalent. A maximum intake of 5 mg will more than suffice to protect the proposed maximum contents of polyunsaturated fatty acids in the order of 1.5 g/100 kcal. Since vitamin E requirements have been reported to increase with the number of double bonds contained in the dietary fatty acid supply (38), the following factors of equivalence should be used to adapt the minimal vitamin E content to the formula fatty acid composition: 0.5 mg α-TE/g linoleic acid (18:2n-6), 0.75 mg α-TE/α-linolenic acid (18:3n-3), 1.0 mg α-TE/g arachidonic acid (20:4n-6), 1.25 mg α-TE/g eicosapentaenoic acid (20:5n-3), and 1.5 mg α-TE/g docosahexaenoic acid (22:6n-3).

Vitamin K

Reference intakes in infancy have been set in the order of 4–10 μg/d (3). Vitamin K levels of current infant formulae, usually above 4 μg/100 kcal, provide an effective protection against vitamin K deficiency and the occurrence of bleeding and may provide a certain level of safety even under some conditions of incomplete vitamin K absorption (39). A population wide daily supplement of 25 μg vitamin K_2 is provided to infants in the Netherlands (40) and oral supplementation of infants with several mg vitamin K is given during the first weeks of life in different countries without any indication of untoward effects. No known toxicities are associated with a formula content of 25 μg/100 kcal (2). Infant formula should contain 4–25 μg/100 kcal.

Water Soluble Vitamins

General Considerations on Minimum and Maximum Levels

Minimum levels of each vitamin in formula, when consumed in normal amounts, should ensure that the infant is able to grow and develop normally and not be at risk of developing an inadequate nutritional status. Minimum levels in infant formulae have been derived from reference nutrient intakes for infants per day based on the model of an infant with a weight of 5 kg and a formula consumption of 500 kcal/d. Maximum levels should ensure that the infant is not exposed to the risk of excess. Since water soluble vitamins supplied in amounts that cannot be utilized or stored by the body must to be excreted, excessive intakes will reduce the margin of safety, especially under conditions of stress, such as during fever or diarrhea or especially during weight loss (41). Tolerance will vary amongst individuals, with age and other circumstances. However, once adequate allowance has been made to ensure that the normal requirements have been met, a reasonable margin of safety would not be expected to require an intake in excess of two to five times the requirement, unless there is clear evidence to justify an alternative. Nutrients added for technological reasons would not be expected to be present in amounts greater than five times the requirement, without clear evidence to justify an alternative. The IEG notes that very high intakes of water soluble vitamins exceeding five times the requirements have generally not been subjected to systematic evaluation in infants with respect to their biologic effects and potential interaction with other formula components, and the safety of such high intakes in infancy has generally not been documented. The IEG sees no reason to add to infant formulae excessive amounts of any nutrient that do not serve any nutritional purpose or provide any other benefit, and the effects of which have not been evaluated. Therefore, the contents of water-soluble vitamins in infant formulae generally should not exceed five times the minimum level.

Thiamin (vitamin B_1)

In view of a reference or adequate intake for infants of 200–300 μg/d (42–44), infant formulae should contain 60–300 μg/100 kcal.

Riboflavin (vitamin B_2)

Considering a reference or adequate intake for infants of 300–400 μg/d (42–44), infant formulae should contain 80–400 μg/100 kcal.

Niacin (vitamin B_3)

Given that niacin contents in human milk have been reported in the range of about 164–343 μg/100 kcal (45), infant formulae should contain 300–1500 μg/100 kcal. These niacin contents of infant formulae apply to preformed niacin.

Pantothenic Acid (vitamin B_5)

Taking a reference or adequate intake for infants of 200–400 μg/d into account (42,43), infant formulae should contain 60–300 μg/100 kcal.

Pyridoxine (vitamin B_6)

Considering mature human milk contents of about 10–45 μg/100 kcal) (45), infant formula contents of 35–175 μg/100 kcal are recommended.

Cobalamin (vitamin B_{12})

Considering average human milk contents (45) and a reference intake for infants of 0.3–0.5 μg/d (42), levels in infant formula should be 0.1–0.5 μg/100 kcal.

Folic Acid

In view of an infant reference or adequate intake of 50–65 μg/d (42,44), infant formula should contain 10–50 μg folic acid/100 kcal.

L-ascorbic Acid (vitamin C)

Human milk contains about 4.5–15 mg/100 kcal (2). Infant reference intakes have been set at 20 mg/d (44), 30 mg/d (2) and 40 mg/d (46). A minimum level in infant formula of 10 mg/100 kcal is recommended. High ascorbic acid intakes may induce copper deficiency (47). Therefore, the maximum level in infant formula should be 30 mg/100 kcal.

Biotin

Taking into account reported human milk contents in the range of about 0.75–1.3 μg/100 kcal (45) and the absence of agreed numerical reference intakes for infants, infant formula levels of 1.5–7.5 μg/100 kcal are recommended.

Minerals and Trace Elements

Iron

The IEG reached unanimous consensus on the iron recommendation as outline below, but after the IEG meeting one member (SB) raised concerns regarding these conclusions and supported the previous recommendation by the national academy of pediatrics in the member's country that infant formula should have a minimal iron content of 4 mg/L (about 0.6 mg/100 kcal) (48). In contrast, all the other 15 IEG members maintained their support for the recommendations made below.

In 1981 the Codex Alimentarius infant formula standard set a requirement of a minimum iron content of 1 mg/100 kcal (1). Recent data indicate that lower iron contents can suffice to meet infant iron requirements. During the period when infant formula may be fed exclusively, i.e. before the introduction of complementary foods, infant formulae based on cows' milk protein supplying about 0.25 mg/100 kcal and 0.6 mg/100 kcal resulted in similar iron status and hematology results (49), while previous studies showed no difference for feeding infant formulae with about 0.6 mg and 1.0 mg/100 kcal, respectively (50). Thus, there was no significant difference between infants fed formulae containing 0.25 mg, 0.6 mg and 1.0 mg per 100 kcal, and there were no infants with inadequate iron status in either group.

After the age of 6 months, infant formula is unlikely to be fed exclusively if at all, and the introduction of complementary feeding/Beikost and the stepwise introduction of foods from adult diets are recommended. The IEG addressed the question whether formula feeding together with diets having very low iron contents might induce a risk of developing iron deficiency anemia during this time period. In a study from Chile (51), infants were fed formulae with about 0.34 mg and 1.9 mg/100 kcal, respectively, from 6 to 12 months of age. As these Chilean infants received little additional iron from complementary feeding, this study evaluates whether the lower level of iron fortification would be inadequate in a poor setting. There was no significant difference in prevalence of iron deficiency anemia between groups. Only iron deficiency (ID) with anemia (IDA) has been associated with adverse functional outcomes. Infants fed the formula with the higher level of iron had somewhat higher levels of serum ferritin, greater mean cell volumes and lower erythrocyte protoporphyrin levels. The authors concluded that formulae with relatively small amounts of iron appear to prevent IDA. It is not at all surprising that formula with a higher level of iron fortification results in higher iron status, but this study provides no evidence for 0.34 mg iron/100 kcal being inadequate for preventing iron deficiency anemia in infants during the first six months of life.

A further consideration addressed was the argument that a low iron bioavailability from formula might justify that the minimum level should be kept higher. It has commonly been assumed that iron absorption from breast milk is much higher (about 5-fold) than from infant formula. However, such data were generated more than two decades ago, and there were several methodological problems with these studies. For example, a commonly cited study by Saarinen et al. (52) used an extrinsic labeling technique that is not valid, and what they called ''formula'' was a homemade product made from cows' milk. In addition, infant formulae have developed during the last two decades and ''current infant formulas have a high iron bioavailability, which is an appealing argument for lowering the level of iron fortification in these products'' (53). Recent studies show that iron absorption from both breast milk and modern infant formulae is about 15–20%; thus, there is no major difference in iron absorption between modern infant formulae and human milk (53–56). Therefore, a breast-fed infant consuming 750 ml of milk will absorb 20% of 0.2–0.3 mg/L = 0.03 – 0.05 mg of iron per day. A formula-fed infant consuming 500 kcal/d would absorb 15–20% of 0.3 mg/100 kcal (proposed minimum for cows' milk based formulae) equal to 0.22 – 0.3 mg of iron per day. Thus, infants fed the proposed minimum level would absorb 4–10 times more iron than breast-fed infants.

The IEG considered potential risks associated with providing too much iron in early life. Prior to the deliberations of LSRO (2) there was little evidence suggesting that too much iron could be detrimental. While both Haschke et al. (57) and Lönnerdal and Hernell (50) had shown lower copper status and copper absorption in infants fed formula with a higher level of iron (1.5 mg/100 kcal and 1 mg/100 kcal, respectively), this had not been associated with any functional outcomes. However, in a recent study on Swedish and Honduran infants (4–9 months of age), Swedish breast-fed infants with adequate iron status, who were given iron supplements, had significantly lower length gain than unsupplemented infants (58). This was not observed for the Honduran cohort as such, but when dividing these infants according to iron status which varied much more in Honduras, infants with adequate iron status given iron supplements had significantly lower length gain. Further, infants with adequate iron status who were given iron had a significantly higher prevalence of diarrhea and a marginally higher prevalence of upper respiratory infections. Thus, in both settings, one affluent and one poor population, providing excess iron caused adverse effects.

While it may be argued that the supplemental iron was given in free form and not in formula, basic studies on

iron homeostasis in infants suggest that there may be reasons for concern, regardless of the form of iron provided. In the Swedish cohort described earlier, iron absorption studies with stable isotopes have been performed (59). Iron absorption at 6 months was identical in infants who had received iron supplements for 2 months and those who had not been supplemented. Thus, at this age there is no homeostatic downregulation of iron absorption as would occur in adults. By 9 months of age, iron absorption was significantly lower in Fe-supplemented infants than in nonsupplemented infants. This shows that regulation of iron absorption is immature at a young age and does not start reaching adult levels until after 9 months of age. This was further supported by the fact that hemoglobin and serum ferritin of infants with adequate iron status increased to the same extent as they did in non-supplemented infants (60), i.e. whatever amounts of iron given will be absorbed and accumulated in the body raising the possibility of iron excess. Whether the adverse effects of excess iron are due to pro-oxidative events caused by Fe, interactions with zinc which may affect insulin like growth factor 1 and thereby growth, or the immune system and be related to infection risks, or other factors cannot be determined with certainty at this time. However, the observed effects warrant caution with respect to supplying iron exceeding requirements. Iron contents higher than 1.3 mg/100 kcal provide no additional benefit, but adverse affects on copper status have been observed (50,57).

A further question addressed was whether a minimum iron content of 0.3 mg/100 kcal would be appropriate for all populations. Various bodies, including the World Health Organization, have made efforts to improve the micronutrient supply of infants with complementary foods globally. In many parts of the world, weaning foods containing meat and iron fortified baby foods with a good bioavailability of iron are commonly used between 6–12 months. Thus, many infants receive quite substantial quantities of iron in their diet, and there may be good reasons to allow formula manufacturers to use a level close to the minimum level. However, in populations where infants are at high risk of iron deficiency, iron contents in infant formula higher than the recommended minimal level seem appropriate.

Phytic acid contained in infant formulae based on soy protein isolates inhibits iron absorption (61), therefore, the minimum and maximum irons level in soy-protein based infant formulae should be about 1.5 times higher than in the cows' milk protein-based formulae. Iron content in infant formulae based on cows' milk protein and its hydrolysates should be in the range of 0.3–1.3 mg/100 kcal, whereas infant formulae based on soy protein isolates should have an iron content of 0.45–2.0 mg/100 kcal. It is emphasized that after the age of about 6 months, other iron containing foods should supplement the iron supplied by formulae. In populations where infants are at high risk of iron deficiency, iron contents in infant formula higher than 0.3 mg/kcal may be appropriate, and national authorities may choose to stipulate iron contents which they consider appropriate.

Calcium

In view of the lower bioavailability of calcium from infant formulae than from cows' milk, and in agreement with previous expert consultations (2,3), a calcium content of 50–140 mg/100 kcal is recommended.

Phosphorus

The bioavailable fraction of total phosphorus contents is about 80% in formulae based on cows' milk proteins and their hydrolysates, and about 70% in soy protein isolate based formulae (2,3). While it is theoretically conceivable to set a level of absorbable phosphorus in infant formulae, the in vivo bioavailability is difficult to determine and no standard method has been established. Therefore, different levels of phosphorus contents in formulae based on cows' milk proteins and their hydrolysates (25–90 mg/100 kcal), and on soy protein isolates (30–100 mg/100 kcal) are recommended.

Calcium-Phosphorus Ratio

In view of possible untoward effects of unbalanced ratios between calcium and phosphorus contents and in line with previous expert consultations (2,3), the calcium-phosphorus-ratio (weight/weight) should not be less than 1:1 and not be greater than 2:1.

Magnesium

Infant formula should contain a minimum similar to human milk contents (about 4.8–5.5 mg/100 kcal) (62), with a range of 5–15 mg/100 kcal.

Sodium, Potassium, Chloride

Infant formula contents similar to those suggested by previous expert consultations (2,3) are recommended: sodium 20–60 mg/100 kcal, potassium 60–160 mg/100 kcal, and chloride 50–160 mg/100 kcal.

Manganese

The recommended minimum level of 1 μg/100 kcal is in the order of human milk concentrations (62). There is no major difference in manganese bioavailability between breast milk and formulae. The maximum content should be 50 μg/100 kcal which is equivalent to that of unsupplemented soy formula, and about 60 times higher than breast milk levels. Higher manganese contents should be avoided, since due to immature manganese excretion in infants they may cause accumulation in tissues including brain and might induce potential

adverse effects, such as neurodevelopmental abnormalities observed in newborn animals (63).

Fluoride

Infants may be exposed to an additional fluoride intake, e.g. from fluoride containing water. The benefit of a high fluoride intake during early infancy is questionable and carries the risk of dental fluorosis. Therefore, maximum levels should be as low as possible and not exceed 60 μg/100 kcal. No minimum level is needed.

Iodine

Considering infant reference nutrient intakes set by different bodies in the range of 35 to 130 μg/d (3) and the range of human milk contents (62), infant formula should contain 10–50 μg/100 kcal.

Selenium

Reported human milk contents vary considerably, with median values in the range of about 0.8 to 3.3 μg/100 kcal (3). Infant reference nutrient intakes set by different bodies range from 5 to 30 μg/d (3). Very high intakes may cause untoward effects (64). Infant formula should contain 1–9 μg/100 kcal.

Copper

Since there is no major difference in bioavailability between human milk and formulae, a minimum level of 35 μg/100 kcal which is similar to breast milk contents is proposed. It appears prudent to limit the concentration of pro-oxidative elements like copper, and a maximum level of 80 μg/100 kcal, about 3 times higher than in human milk, is recommended.

Zinc

Reference nutrient intakes for infants range from 1–5 mg/d. Even though there is a difference in bioavailability between formulae based on cows' milk proteins and on soy protein isolates, respectively, one single minimum value of 0.5 mg/100 kcal is considered sufficient as it will cover the need of zinc also in infants fed soy formula. Since high intakes may interfere with the absorption and metabolism of other micronutrients, a maximum level of 1.5 mg/100 kcal is set.

Other Substances

Choline

In accordance with the conclusions of previous expert reviews (2,3), a minimum choline content of 7 mg/100 kcal is recommended. LSRO and SCF recommended maximum levels of 30 mg/100 kcal based on extrapolation of adult data. Since no major safety concerns exist and no adverse effects of higher choline intakes have been documented in infants, we suggest a maximum level of 50 mg/100 kcal to harmonize the maximum choline content with a proposed maximum phospholipid content of 300 mg/100 kcal (see optional ingredients, below), considering that a major part of added phospholipids may be provided as phosphatidyl choline.

Myo-inositol

The recommendations of previous expert reviews (2,3) for a myo-inositol content of 4–40 mg/100 kcal are supported.

L-carnitine

The recommendations of previous expert reviews (2,3) for a minimum L-carnitine content of 1.2 mg/100 kcal are supported. In contrast to the SCF, LSRO suggested a maximum level of 2 mg/100 kcal based on the upper end of the usual range found in human milk (2). In the absence of indications of any untoward effects of higher L-carnitine intakes in infants, the IEG concluded that no maximum level is needed to be set.

Optional Ingredients

Taurine

In line with previous expert consultations (2,3), the IEG sees no need for mandatory addition of taurine to infant formulae, but recommends the optional addition in amounts up to 12 mg/100 kcal.

Nucleotides

Several publications have reported beneficial effects of the addition of nucleotides to infant formulae (2,3). The IEG did not find sufficient data to support additional benefits from increasing intakes to levels greater than 5 mg/100 kcal, while adverse affects of higher contents such as increased risk of respiratory tract infections have been reported (65). The optional addition of nucleotides at a maximum total content of 5 mg/100 kcal as well as maximal levels of 2.5 mg/100 kcal CMP, 1.75 mg/100 kcal UMP, 1.5 mg/100 kcal AMP, 0.5 mg/100 kcal GMP, and 1.0 mg/100 kcal IMP are recommended.

Phospholipids

Phospholipids such as phosphatidyl choline have key functions in signal transduction affecting important cell functions. In milk and in the intestinal lumen phospholipids contribute to solubilizing lipophilic compounds. Phospholipids may also be added to infant formulae as a source of long-chain polyunsaturated fatty acids. A

maximum concentration of 300 mg/100 kcal (equivalent to about 2 g/L) seems safe with respect to the potential range obtained of triglyceride/phospholipids ratios.

Long-Chain Polyunsaturated Fatty Acids (LC-PUFA)

In view of beneficial effects of the addition of LC-PUFA to infant formulae reported in a number of publications (2,3), their optional addition to infant formulae is supported by the IEG. Docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (AA, 20:4n-6) are the main LC-PUFA in human milk, both of which are always present (66). The DHA contents in human milk are quite variable and reach high levels in populations with high marine food consumption, with consecutive marked variation of the DHA to AA ratio in milk (66–68). LC-PUFA of the n-3 series such as DHA and of the n-6 series such as AA, respectively, are metabolic competitors with differential effects for example on eicosanoid metabolism, membrane physiology, and immune function. Eicosapentaenoic acid (EPA, 20:5n-3) is found in only minor concentrations in human milk and infant tissues and is a direct metabolic competitor of AA. A large number of studies in which LC-PUFA were added to infant formulae have not raised major safety concerns and a recent meta-analysis found no indication of adverse effects on growth of the addition of both DHA and AA, and neither were adverse effects reported in analyzing the limited number of studies with addition of only n-3 LC-PUFA (69). However, adverse growth effects have been reported in single studies with supplementation of fish oils without concomitant n-6 LC-PUFA supply, particularly at high EPA intakes (69). It is noted that at this time there is no sufficient documentation of the benefits and safety of the addition of DHA to infant formula at levels $>0.5\%$ of total fat content, or of DHA without concomitant addition of AA. Until the benefits and suitability for particular nutritional uses and the safety of other additions have been adequately demonstrated, the optional addition of DHA should not exceed 0.5% of total fat intake, and AA contents should be at least the same concentration as DHA, whereas the content of EPA in infant formula should not exceed the DHA content.

Carrageenan

The IEG noted that carrageenan is included in the provisional list of accepted food additives for infant formulae of the current draft of the Codex Alimentarius for an infant formula standard. Carrageenan is used as a thickener, stabilizer, and textures in a variety of processed foods. In animals carrageenan can induce inflammatory reactions in the intestine. As a component of a barium enema solution, carrageenan produced allergic reactions (70). Given the lack of adequate information on possible absorption of carrageenan by the immature gut in the young infants and its biologic effects in infancy, it appears inadvisable to use carrageenan in infant formulae intended for feeding young infants, including those in the category of foods for special medical purposes.

GLOSSARY ABBREVIATIONS

CCNFSDU, Codex Committee on Nutrition and Foods for Special Dietary Uses

ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition

EWG, Electronic working group of CCNFSDU

FAO, Food and Agriculture Organization of the United Nations

FISPGHAN, Federation of International Societies of Pediatric Gastroenterology, Hepatology and Nutrition

FSMP, Food for special medical purposes

LSRO, Life Science Research Office, American Society for Nutritional Sciences

ID, Iron deficiency

IDA, Iron deficiency anemia

IEG, ESPGHAN coordinated International Expert Group

NPN, Nonprotein nitrogen

RE, Retinol equivalent

SCF, Scientific Committee for Food of the European Commission

TE, Tocopherol equivalent

WHO, World Health Organization

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(Acts whose publication is obligatory)

COMMISSION DIRECTIVE 2006/141/EC

of 22 December 2006

on infant formulae and follow-on formulae and amending Directive 1999/21/EC

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Council Directive 89/398/EEC of 3 May 1989 on the approximation of the laws of the Member States relating to foodstuffs intended for particular nutritional uses [1], and in particular Article 4(1) thereof,

After consulting the European Food Safety Authority (the Authority),

Whereas:

(1) Directive 89/398/EEC concerns foodstuffs intended for particular nutritional uses. The specific provisions applicable to certain groups of foods for particular nutritional uses are laid down by specific Directives.

(2) Commission Directive 91/321/EEC of 14 May 1991 on infant formulae and follow-on formulae [2] is a specific Directive adopted pursuant to Directive 89/398/EEC. That Directive has been substantially amended several times [3]. Since further amendments are to be made, it should be recast in the interests of clarity.

(3) In the light of discussions in international fora, in particular Codex Alimentarius, in relation to the timing of the introduction of complementary foods into the diet of infants, it is appropriate to amend the current definitions of infant formulae and follow-on formulae and certain provisions on the labelling of follow-on formulae in Directive 91/321/EEC.

(4) Infant formula is the only processed foodstuff which wholly satisfies the nutritional requirements of infants during the first months of life until the introduction of appropriate complementary feeding. In order to safeguard the health of such infants it is necessary to ensure that the only products marketed as suitable for such use during the period would be infant formulae.

(5) The essential composition of infant formulae and follow-on formulae must satisfy the nutritional requirements of infants in good health as established by generally accepted scientific data.

(6) The requirements concerning the essential composition of infant formulae and follow-on formulae should include detailed provisions on the protein content. Notwithstanding that traditionally different appropriate conversion factors have been used for the calculation of the protein content from the nitrogen content of different protein sources, recent scientific advice indicates that for the specific purposes of calculating the protein content of infant formulae and follow-on formulae it is appropriate to use a single conversion factor adapted to these products. As infant formulae and follow-on formulae are sophisticated products that are specially formulated for their intended purpose, additional essential requirements on protein, including minimum and maximum levels of protein and minimum levels of certain amino acids, should be established. The protein requirements specified in this Directive should relate to the final products as such, prepared ready for consumption.

[1] OJ L 186, 30.6.1989, p. 27. Directive as last amended by Regulation (EC) No 1882/2003 of the European Parliament and of the Council (OJ L 284, 31.10.2003, p. 1).
[2] OJ L 175, 4.7.1991, p. 35. Directive as last amended by the 2003 Act of Accession.
[3] See Annex X, Part A.

(7) On the basis of such data, the essential composition of infant formulae and follow-on formulae manufactured from cows' milk proteins and soya proteins alone or in a mixture, as well as infant formulae based on protein hydrolysates, can already be defined. The same is not true for preparations based wholly or partly on other sources of protein. For this reason specific rules for such products, if necessary, should be adopted at a later date.

(8) It is important that ingredients used in the manufacture of infant formulae and follow-on formulae are suitable for the particular nutritional use by infants and that their suitability has been demonstrated, when necessary, by appropriate studies. Guidance on the design and conduct of appropriate studies has been published by expert scientific groups such as the Scientific Committee on Food, the UK Committee on the Medical Aspects of Food and Nutrition Policy, and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition. Such guidance should be taken into consideration when ingredients are introduced into infant formulae or follow-on formulae.

(9) A number of the substances that may be used in the manufacture of infant formulae and follow-on formulae may also be used in foodstuffs as food additives. In that context, purity criteria have already been or are to be adopted at Community level in accordance with Council Directive 89/107/EEC of 21 December 1988 on the approximation of the laws of the Member States concerning food additives authorised for use in foodstuffs intended for human consumption ([1]). Those purity criteria should apply to those substances whatever the purpose of their use in foodstuffs.

(10) Pending the adoption of purity criteria for substances for which such criteria have not yet been adopted at Community level, and in order to ensure a high level of protection for public health, generally acceptable purity criteria recommended by international organisations or agencies, such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) or European Pharmacopoeia (EUP), should apply. In addition, Member States should be permitted to maintain national rules setting stricter purity criteria.

([1]) OJ L 40, 11.2.1989, p. 27. Directive as last amended by Regulation (EC) No 1882/2003.

(11) Given the particular nature of infant formula, additional means to those usually available to monitoring bodies should be available in order to facilitate efficient monitoring of those products.

(12) Infant formulae based on protein hydrolysates are distinct from semi-elemental diet products based on high degree hydrolysates used for the dietary management of diagnosed medical conditions, which are not covered by this Directive.

(13) This Directive reflects current knowledge about the products concerned. Any amendment, to allow innovation based on scientific and technical progress, should be decided by the procedure referred to in Article 13(2) of Directive 89/398/EEC.

(14) Maximum levels for pesticide residues set out in relevant Community legislation, in particular Council Directive 76/895/EEC of 23 November 1976 relating to the fixing of maximum levels for pesticide residues in and on fruit and vegetables ([2]), in Council Directive 86/362/EEC of 24 July 1986 on the fixing of maximum levels for pesticide residues in and on cereals ([3]), in Council Directive 86/363/EEC of 24 July 1986 on the fixing of maximum levels for pesticide residues in and on foodstuffs of animal origin ([4]), and in Council Directive 90/642/EEC of 27 November 1990 on the fixing of maximum levels for pesticide residues in and on certain products of plant origin, including fruit and vegetables ([5]), should apply without prejudice to specific provisions set out in this Directive.

(15) Taking into account the Community's international obligations, in cases where the relevant scientific evidence is insufficient, the precautionary principle referred to in Article 7 of Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety ([6]) allows the Community to provisionally adopt measures on the basis of available pertinent information, pending an additional assessment of risk and a review of the measure within a reasonable period of time.

([2]) OJ L 340, 9.12.1976, p. 26. Directive as last amended by Commission Directive 2006/92/EC (OJ L 311, 10.11.2006, p. 31).
([3]) OJ L 221, 7.8.1986, p. 37. Directive as last amended by Directive 2006/92/EC.
([4]) OJ L 221, 7.8.1986, p. 43. Directive as last amended by Commission Directive 2006/62/EC (OJ L 206, 27.7.2006, p. 27).
([5]) OJ L 350, 14.12.1990, p. 71. Directive as last amended by Directive 2006/92/EC.
([6]) OJ L 31, 1.2.2002, p. 1. Regulation as last amended by Commission Regulation (EC) No 575/2006 (OJ L 100, 8.4.2006, p. 3).

(16) On the basis of the two opinions given by the Scientific Committee for Food on 19 September 1997 and 4 June 1998, there are at present doubts as to the adequacy of existing acceptable daily intake (ADI) values of pesticides and pesticide residues for the protection of the health of infants and young children. Therefore, as far as foodstuffs for particular nutritional uses intended for infants and young children are concerned, it is appropriate to adopt a very low common limit for all pesticides. This very low common limit should be fixed at 0,01 mg/kg which normally is in practice the minimum detectable level.

(17) Severe limitations on pesticide residues should be required. With careful selection of raw materials, and given that infant formulae and follow-on formulae undergo extensive processing during their manufacture, it is feasible to produce products containing very low levels of pesticide residues. However, in the case of a small number of pesticides or metabolites of pesticides even a maximum residue level of 0,01 mg/kg might, under worst-case intake conditions, allow infants and young children to exceed the ADI. This is the case for pesticides or metabolites of pesticides with an ADI lower than 0,0005 mg/kg body weight.

(18) This Directive should establish the principle of the prohibition of the use of these pesticides in the production of agricultural products intended for infant formulae and follow-on formulae. However, this prohibition does not necessarily guarantee that products are free from such pesticides, since some pesticides contaminate the environment and their residues may be found in the products concerned.

(19) Most of the pesticides which have ADI values lower than 0,0005 mg/kg body weight are already prohibited in the Community. The prohibited pesticides should not be detectable in infant formulae and follow-on formulae by state-of-the-art analytical methods. However, some pesticides degrade slowly and still contaminate the environment. They might be present in infant formulae and follow-on formulae even if they have not been used. For the purposes of control, a harmonised approach should be followed.

(20) Pending Commission decisions on whether they satisfy the safety requirements of Article 5 of Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market [1], the continued use of authorised pesticides should be permitted as long as their residues comply with the maximum residue levels established in this Directive. The latter should be set at levels ensuring that their respective ADI values are not exceeded by infants and young children under worst-case intake conditions.

(21) The Annexes to this Directive dealing with pesticides should be amended following the completion of the review programme being carried out under Directive 91/414/EEC.

(22) Pursuant to Article 7(1) of Directive 89/398/EEC, the products covered by this Directive are subject to the general rules laid down by Directive 2000/13/EC of the European Parliament and of the Council of 20 March 2000 on the approximation of the laws of the Member States relating to the labelling, presentation and advertising of foodstuffs [2]. This Directive adopts and expands upon the additions and exceptions to those general rules, where it is appropriate, in order to promote and protect breast feeding.

(23) In particular, the nature and destination of the products covered by this Directive require nutritional labelling showing the energy value and principal nutrients they contain. On the other hand, the method of use should be specified in accordance with point 9 of Article 3(1) and Article 11(2) of Directive 2000/13/EC, in order to prevent inappropriate uses likely to be detrimental to the health of infants.

(24) Given the nature of infant formulae and follow-on formulae the detailed rules as to nutrient declaration on the labelling need to be clarified in order to avoid any problems which may arise from the application of other relevant Community legislation.

(25) Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on food [3] establishes the rules and conditions for the use of nutrition and health claims concerning foods. However, Article 1(5) of that Regulation states that it shall apply without prejudice to, in particular, Directive 89/398/EEC and directives adopted relating to foodstuffs for particular nutritional uses.

(26) It is appropriate to set out specific conditions for the use of nutrition and health claims concerning infant formulae in this Directive. In this respect, it is necessary, in order to supply objective and scientifically verified information, to define the conditions under which nutrition and health claims are authorised, and to establish a list of authorised claims. In accordance with the third subparagraph of Article 4(1) of Directive 89/398/EEC, modification of that list of nutrition and health claims should be adopted, when necessary, after consultation of the Authority.

[1] OJ L 230, 19.8.1991, p. 1. Directive as last amended by Commission Directive 2006/85/EC (OJ L 293, 24.10.2006, p. 3).

[2] OJ L 109, 6.5.2000, p. 29. Directive as last amended by Directive 2003/89/EC (OJ L 308, 25.11.2003, p. 15) .

[3] OJ L 404, 30.12.2006, p. 9.

(27) In an effort to provide better protection for the health of infants, the rules of composition, labelling and advertising laid down in this Directive should be in conformity with the principles and the aims of the International Code of Marketing of Breast-milk Substitutes adopted by the 34th World Health Assembly, bearing in mind the particular legal and factual situations existing in the Community.

(28) Given the important role which information on infant feeding plays in choosing, by pregnant women and mothers of infants, the type of nourishment provided to their children, it is necessary for Member States to take appropriate measures in order that this information ensures an adequate use of the products in question and is not counter to the promotion of breast feeding.

(29) This Directive does not concern the conditions of sale of publications specialising in baby care and of scientific publications.

(30) Commission Directive 1999/21/EC of 25 March 1999 on dietary foods for special medical purposes [1] lays down compositional and labelling requirements for dietary foods for special medical purposes. The Annex to that Directive sets out values for minerals in nutritionally complete foods intended for use by infants. There has been new scientific advice as regards the minimum level of manganese in foods intended for infants. Therefore, it is appropriate to amend the levels of manganese in dietary foods for special medical purposes intended for infants set out in that Annex. Directive 1999/21/EC should therefore be amended accordingly.

(31) Due to the specific nature of dietary foods for special medical purposes intended for infants and to the necessity to assess the new formulation of such products, manufacturers require a longer period to adapt their products to the essential composition that derive from the new requirements set out in this Directive.

(32) The obligation to transpose this Directive into national law should be confined to those provisions which represent a substantive change as compared with the earlier Directive. The obligation to transpose the provisions which are unchanged arises under the earlier Directive.

[1] OJ L 91, 7.4.1999, p. 29. Directive as amended by the 2003 Act of Accession.

(33) This Directive should be without prejudice to the obligations of the Member States relating to the time limits for transposition into national law of the Directives set out in Annex X, Part B.

(34) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on the Food Chain and Animal Health,

HAS ADOPTED THIS DIRECTIVE:

Article 1

This Directive is a 'specific Directive' within the meaning of Article 4(1) of Directive 89/398/EEC and lays down compositional and labelling requirements for infant formulae and follow-on formulae intended for use by infants in good health in the Community.

It also provides for Member States to give effect to principles and aims of the International Code of Marketing of Breast-milk Substitutes dealing with marketing, information and responsibilities of health authorities.

Article 2

For the purposes of this Directive, the definitions of 'claim', 'nutrition claim', 'health claim' and 'reduction of disease risk claim' in Article 2(2)(1), (4), (5) and (6) of Regulation (EC) No 1924/2006 shall apply.

The following definitions shall also apply:

(a) 'infants' means children under the age of 12 months;

(b) 'young children' means children aged between one and three years;

(c) 'infant formulae' means foodstuffs intended for particular nutritional use by infants during the first months of life and satisfying by themselves the nutritional requirements of such infants until the introduction of appropriate complementary feeding;

(d) 'follow-on formulae' means foodstuffs intended for particular nutritional use by infants when appropriate complementary feeding is introduced and constituting the principal liquid element in a progressively diversified diet of such infants;

(e) 'pesticide residue' means the residue in infant formulae and follow-on formulae of a plant protection product, as defined in point 1 of Article 2 of Directive 91/414/EEC, including its metabolites and products resulting from its degradation or reaction.

Article 3

Infant formulae and follow-on formulae may be marketed within the Community only if they comply with this Directive.

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 until the introduction of appropriate complementary feeding.

Article 4

Infant formulae and follow-on formulae shall not contain any substance in such quantity as to endanger the health of infants and young children.

Article 5

Infant formulae shall be manufactured from protein sources defined in point 2 of Annex I and other food ingredients, as the case may be, whose suitability for particular nutritional use by infants from birth has been established by generally accepted scientific data.

Such suitability shall be demonstrated through a systematic review of the available data relating to the expected benefits and to safety considerations as well as, where necessary, appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

Article 6

Follow-on formulae shall be manufactured from protein sources defined in point 2 of Annex II and other food ingredients, as the case may be, whose suitability for particular nutritional use by infants aged over six months has been established by generally accepted scientific data.

Such suitability shall be demonstrated through a systematic review of the available data relating to the expected benefits and to safety considerations as well as, where necessary, appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

Article 7

1. Infant formulae shall comply with the compositional criteria set out in Annex I taking into account the specifications in Annex V.

In the case of infant formulae manufactured from cows' milk proteins defined in point 2.1 of Annex I with a protein content between the minimum and 0,5 g/100 kJ (2 g/100 kcal), the suitability of the infant formula for the particular nutritional use by infants shall be demonstrated through appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

In the case of infant formulae manufactured from protein hydrolysates defined in point 2.2 of Annex I with a protein content between the minimum and 0,56 g/100 kJ (2,25 g/100 kcal), the suitability of the infant formula for the particular nutritional use by infants shall be demonstrated through appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies and shall be in accordance with the appropriate specifications set out in Annex VI.

2. Follow-on formulae shall comply with the compositional criteria set out in Annex II taking into account the specifications set out in Annex V.

3. In order to make infant formulae and follow-on formulae ready for use, nothing more shall be required, as the case may be, than the addition of water.

4. The prohibitions and limitations on the use of food ingredients in infant formulae and follow-on formulae set out in Annexes I and II shall be observed.

Article 8

1. Only the substances listed in Annex III may be used in the manufacture of infant formulae and follow-on formulae in order to satisfy the requirements on:

(a) mineral substances;

(b) vitamins;

(c) amino acids and other nitrogen compounds;

(d) other substances having a particular nutritional purpose.

2. Purity criteria for substances, as provided for in Community legislation concerning the use of substances listed in Annex III, in the manufacture of foodstuffs for purposes other than those covered by this Directive, shall apply.

3. For those substances for which no purity criteria have been provided for in Community legislation, generally acceptable purity criteria recommended by international bodies shall apply until the adoption of such criteria at Community level.

However, national rules setting stricter purity criteria than those recommended by international bodies may be maintained.

Article 9

1. To facilitate the efficient official monitoring of infant formulae, when a food business operator places an infant formula on the market he shall notify the competent authority of the Member States where the product is being marketed by forwarding to it a model of the label used for the product.

2. The competent authorities for the purposes of this Article are those referred to in Article 9(4) of Directive 89/398/EEC.

Article 10

1. Infant formulae and follow-on formulae shall not contain residues of individual pesticides at levels exceeding 0,01 mg/kg of the product as proposed ready for consumption or as reconstituted according to the instructions of the manufacturer.

Analytical methods for determining the levels of pesticide residues shall be generally acceptable standardised methods.

2. The pesticides listed in Annex VIII shall not be used in agricultural products intended for the production of infant formulae and follow-on formulae.

However, for the purpose of controls:

(a) pesticides listed in Table 1 of Annex VIII are considered not to have been used if their residues do not exceed a level of 0,003 mg/kg. This level, which is considered to be the limit of quantification of the analytical methods, shall be kept under regular review in the light of technical progress;

(b) pesticides listed in Table 2 of Annex VIII are considered not to have been used if their residues do not exceed a level of 0,003 mg/kg. This level shall be kept under regular review in the light of data on environmental contamination.

3. By way of derogation from paragraph 1, for the pesticides listed in Annex IX, the maximum residue levels specified therein shall apply.

4. The levels referred to in paragraphs 2 and 3 shall apply to the products as proposed ready for consumption or as reconstituted according to the instructions of the manufacturers.

Article 11

Except as provided for in Article 12, the name under which infant formulae and follow-on formulae are sold shall be, respectively:

— *in Bulgarian*: 'храни за кърмачета' and 'преходни храни',

— *in Spanish*: 'Preparado para lactantes' and 'Preparado de continuación',

— *in Czech*: 'počáteční kojenecká výživa' and 'pokračovací kojenecká výživa',

— *in Danish*: 'Modermælkserstatning' and 'Tilskudsblanding',

— *in German*: 'Säuglingsanfangsnahrung' and 'Folgenahrung',

— *in Estonian*: 'imiku piimasegu' and 'jätkupiimasegu',

— *in Greek*: 'Παρασκεύασμα για βρέφη' and 'Παρασκεύασμα δεύτερης βρεφικής ηλικίας',

— *in English*: 'infant formula' and 'follow-on formula',

— *in French*: 'Préparation pour nourrissons' and 'Préparation de suite',

— *in Italian*: 'Alimento per lattanti' and 'Alimento di proseguimento',

— *in Latvian*: 'Mākslīgais maisījums zīdaiņiem' un 'Mākslīgais papildu ēdināšanas maisījums zīdaiņiem',

— *in Lithuanian*: 'mišinys kūdikiams iki papildomo maitinimo įvedimo' and 'mišinys kūdikiams, įvedus papildomą maitinimą',

— *in Hungarian*: 'anyatej-helyettesítő tápszer' and 'anyatej-kiegészítő tápszer',

— *in Maltese*: 'formula tat-trabi' and 'formula tal-prosegwiment',

— *in Dutch*: 'Volledige zuigelingenvoeding' and 'Opvolgzuigelingenvoeding',

— *in Polish*: 'preparat do początkowego żywienia niemowląt' and 'preparat do dalszego żywienia niemowląt',

— *in Portuguese*: 'Fórmula para lactentes' and 'Fórmula de transição',

— *in Romanian*: 'preparate pentru sugari' and 'preparate pentru copii de vârstă mică',

— *in Slovak*: 'počiatočná dojčenská výživa' and 'následná dojčenská výživa'.

— *in Slovenian*: 'začetna formula za dojenčke' and 'nadaljevalna formula za dojenčke',

— *in Finnish*: 'Äidinmaidonkorvike' and 'Vieroitusvalmiste',

— *in Swedish*: 'Modersmjölksersättning' and 'Tillskottsnäring'.

Article 12

The name under which infant formulae and follow-on formulae manufactured entirely from cows' milk proteins are sold, shall be respectively:

— *in Bulgarian*: 'млека за кърмачета' and 'преходни млека',

— *in Spanish*: 'Leche para lactantes' and 'Leche de continuación',

— *in Czech*: 'počáteční mléčná kojenecká výživa' and 'pokračovací mléčná kojenecká výživa',

— *in Danish*: 'Modermælkserstatning udelukkende baseret på mælk' and 'Tilskudsblanding udelukkende baseret på mælk',

— *in German*: 'Säuglingsmilchnahrung' and 'Folgemilch',

— *in Estonian*: 'Piimal põhinev imiku piimasegu' and 'Piimal põhinev jätkupiimasegu',

— *in Greek*: 'Τάλα για βρέφη' and 'Τάλα δεύτερης βρεφικής ηλικίας',

— *in English*: 'infant milk' and 'follow-on milk',

— *in French*: 'Lait pour nourrissons' and 'Lait de suite',

— *in Italian*: 'Latte per lattanti' and 'Latte di proseguimento',

— *in Latvian*: 'Mākslīgais piena maisījums zīdaiņiem' un 'Mākslīgais papildu ēdināšanas piena maisījums zīdaiņiem',

— *in Lithuanian*: 'pieno mišinys kūdikiams iki papildomo maitinimo įvedimo' and 'pieno mišinys kūdikiams įvedus papildomą maitinimą',

— *in Hungarian*: 'tejalapú anyatej-helyettesítő tápszer' and 'tejalapú anyatej-kiegészítő tápszer',

— *in Maltese*: 'ħalib tat-trabi' and 'ħalib tal-prosegwiment',

— *in Dutch*: 'Volledige zuigelingenvoeding op basis van melk' or 'Zuigelingenmelk' and 'Opvolgmelk',

— *in Polish*: 'mleko początkowe' and 'mleko następne',

— *in Portuguese*: 'Leite para lactentes' and 'Leite de transição',

— *in Romanian*: 'lapte pentru sugari' and 'lapte pentru copii de vârstă mică';

— *in Slovak*: 'počiatočná dojčenská mliečna výživa' and 'následná dojčenská mliečna výživa',

— *in Slovenian*: 'začetno mleko za dojenčke' and 'nadaljevalno mleko za dojenčke',

— *in Finnish*: 'Maitopohjainen äidinmaidonkorvike' and 'Maitopohjainen vieroitusvalmiste',

— *in Swedish*: 'Modersmjölksersättning uteslutande baserad på mjölk' and 'Tillskottsnäring uteslutande baserad på mjölk'.

Article 13

1. The labelling shall bear, in addition to those provided for in Article 3(1) of Directive 2000/13/EC, the following mandatory particulars:

(a) in the case of infant formulae, a statement to the effect that the product is suitable for particular nutritional use by infants from birth when they are not breast fed;

(b) in the case of follow-on formulae, a statement to the effect that the product is suitable only for particular nutritional use by infants over the age of six months, that it should form only part of a diversified diet, that it is not to be used as a substitute for breast milk during the first six months of life and that the decision to begin complementary feeding, including any exception to six months of age, should be made only on the advice of independent persons having qualifications in medicine, nutrition or pharmacy, or other professionals responsible for maternal and child care, based on the individual infant's specific growth and development needs;

(c) in the case of infant formulae and follow-on formulae, the available energy value, expressed in kJ and kcal, and the content of proteins, carbohydrates and lipids, expressed in numerical form, per 100 ml of the product ready for use;

(d) in the case of infant formulae and follow-on formulae, the average quantity of each mineral substance and of each vitamin mentioned in Annexes I and II respectively, and where applicable of choline, inositol and carnitine, expressed in numerical form, per 100 ml of the product ready for use;

(e) in the case of infant formulae and follow-on formulae, instructions for appropriate preparation, storage and disposal of the product and a warning against the health hazards of inappropriate preparation and storage.

2. The labelling may bear the following particulars:

(a) for infant formulae and follow-on formulae the average quantity of nutrients mentioned in Annex III when such declaration is not covered by paragraph 1(d) of this Article, expressed in numerical form, per 100 ml of the product ready for use;

(b) for follow-on formulae in addition to numerical information, information on vitamins and minerals included in Annex VII, expressed as a percentage of the reference values given therein, per 100 ml of the product ready for use.

3. The labelling of infant formulae and follow-on formulae shall be designed to provide the necessary information about the appropriate use of the products so as not to discourage breast feeding.

The use of the terms 'humanised', 'maternalised', 'adapted', or similar terms shall be prohibited.

4. The labelling of infant formulae shall, in addition, bear the following mandatory particulars, preceded by the words 'Important Notice' or their equivalent:

(a) a statement concerning the superiority of breast feeding;

(b) a statement recommending that the product be used only on the advice of independent persons having qualifications in medicine, nutrition or pharmacy, or other professionals responsible for maternal and child care.

5. The labelling of infant formulae shall not include pictures of infants, nor shall it include other pictures or text which may idealise the use of the product. It may, however, have graphic representations for easy identification of the product and for illustrating methods of preparation.

6. The labelling of infant formulae may bear nutrition and health claims only in the cases listed in Annex IV and in accordance with the conditions set out therein.

7. Infant formulae and follow-on formulae shall be labelled in such a way that it enables consumers to make a clear distinction between such products so as to avoid any risk of confusion between infant formulae and follow-on formulae.

8. The requirements, prohibitions and restrictions referred to in paragraphs 3 to 7 shall also apply to:

(a) the presentation of the products concerned, in particular their shape, appearance or packaging, the packaging materials used, the way in which they are arranged and the setting in which they are displayed;

(b) advertising.

Article 14

1. Advertising of infant formulae shall be restricted to publications specialising in baby care and scientific publications. Member States may further restrict or prohibit such advertising. Such advertisements for infant formulae shall be subject to the conditions laid down in Article 13(3) to (7) and Article 13(8)(b) and contain only information of a scientific and factual nature. Such information shall not imply or create a belief that bottle-feeding is equivalent or superior to breast feeding.

2. There shall be no point-of-sale advertising, giving of samples or any other promotional device to induce sales of infant formula directly to the consumer at the retail level, such as special displays, discount coupons, premiums, special sales, loss-leaders and tie-in sales.

3. Manufacturers and distributors of infant formulae shall not provide, to the general public or to pregnant women, mothers or members of their families, free or low-priced products, samples or any other promotional gifts, either directly or indirectly via the health care system or health workers.

Article 15

1. Member States shall ensure that objective and consistent information is provided on infant and young child feeding for use by families and those involved in the field of infant and young child nutrition covering the planning, provision, design and dissemination of information and their control.

2. Member States shall ensure that informational and educational materials, whether written or audiovisual, dealing with the feeding of infants and intended to reach pregnant women and mothers of infants and young children, shall include clear information on all the following points:

(a) the benefits and superiority of breast feeding;

(b) maternal nutrition and the preparation for and maintenance of breast feeding;

(c) the possible negative effect on breast feeding of introducing partial bottle feeding;

(d) the difficulty of reversing the decision not to breast feed;

(e) where needed, the proper use of infant formulae.

When such materials contain information about the use of infant formulae, they shall include the social and financial implications of its use, the health hazards of inappropriate foods or feeding methods, and, in particular, the health hazards of improper use of infant formulae. Such material shall not use any pictures which may idealise the use of infant formulae.

3. Member States shall ensure that donations of informational or educational equipment or materials by manufacturers or distributors shall be made only on request and with the written approval of the appropriate national authority or within guidelines given by that authority for this purpose. Such equipment or materials may bear the donating company's name or logo, but shall not refer to a proprietary brand of infant formulae and shall be distributed only through the health care system.

4. Member States shall ensure that donations or low-price sales of supplies of infant formulae to institutions or organisations, whether for use in the institutions or for distribution outside them, shall only be used by or distributed for infants who have to be fed on infant formulae and only for as long as required by such infants.

Article 16

In the Annex to Directive 1999/21/EC, the row relating to manganese set out in the second part of Table I concerning minerals, is replaced by the following:

'Manganese (µg)	0,25	25	1	100'

Article 17

The new requirements set out in Article 7(1) and (2) of this Directive shall not apply mandatorily to dietary foods for special medical purposes intended specifically for infants, as referred to in point 4 of the Annex to Directive 1999/21/EC, until 1 January 2012.

Article 18

1. Member States shall adopt and publish, by 31 December 2007 at the latest, the laws, regulations and administrative provisions necessary to comply with Articles 2, 3 and 5 to 17 and Annexes I to VII. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

They shall apply those provisions in such a way as to:

— permit trade in products complying with this Directive by 1 January 2008 at the latest,

— without prejudice to Article 17, prohibit, with effect from 31 December 2009 trade in products which do not comply with this Directive.

When Member States adopt those provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. They shall also include a statement that references in existing laws, regulations and administrative provisions to the Directive repealed by this Directive shall be construed as references to this Directive. Member States shall determine how such reference is to be made and how that statement is to be formulated.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 19

Directive 91/321/EEC, as amended by the Directives listed in Annex X, Part A, is repealed with effect from 1 January 2008, without prejudice to the obligations of the Member States relating to the time limits for transposition into national law of the Directives listed in Annex X, Part B.

References to the repealed Directive shall be construed as references to this Directive and shall be read in accordance with the correlation table in Annex XI.

Article 20

This Directive shall enter into force on the 20th day following its publication in the *Official Journal of the European Union*.

Article 21

This Directive is addressed to the Member States.

Done at Brussels, 22 December 2006.

For the Commission
Markos KYPRIANOU
Member of the Commission

ANNEX I

ESSENTIAL COMPOSITION OF INFANT FORMULAE WHEN RECONSTITUTED AS INSTRUCTED BY THE MANUFACTURER

The values set out in this Annex refer to the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer.

1. ENERGY

Minimum	Maximum
250 kJ/100 ml (60 kcal/100 ml)	295 kJ/100 ml (70 kcal/100 ml)

2. PROTEINS

(Protein content = nitrogen content × 6,25)

2.1 **Infant formulae manufactured from cows' milk proteins**

Minimum ([1])	Maximum
0,45 g/100 kJ (1,8 g/100 kcal)	0,7 g/100 kJ (3 g/100 kcal)

([1]) Infant formulae manufactured from cows' milk protein with a protein content between the minimum and 0,5 g/100 kJ (2 g/100 kcal) shall be in accordance with the second subparagraph of Article 7(1).

For an equal energy value, the infant formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 2, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2. The ratio of methionine:cystine may be greater than 2 but shall not be greater than 3 provided that the suitability of the product for the particular nutritional use by infants is demonstrated through appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

2.2 **Infant formulae manufactured from protein hydrolysates**

Minimum ([1])	Maximum
0,45 g/100 kJ (1,8 g/100 kcal)	0,7 g/100 kJ (3 g/100 kcal)

([1]) Infant formulae manufactured from protein hydrolysates with a protein content between the minimum and 0,56 g/100 kJ (2,25 g/100 kcal) shall be in accordance with the third subparagraph of Article 7(1).

For an equal energy value, the infant formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 2, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2. The ratio of methionine:cystine may be greater than 2 but shall not be greater than 3 provided that the suitability of the product for the particular nutritional use by infants is demonstrated through appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

The L-carnitine content shall be at least equal to 0,3 mg/100 kJ (1,2 mg/100 kcal).

2.3 **Infant formulae manufactured from soya protein isolates, alone or in a mixture with cows' milk proteins**

Minimum	Maximum
0,56 g/100 kJ (2,25 g/100 kcal)	0,7 g/100 kJ (3 g/100 kcal)

Only protein isolates from soya shall be used in manufacturing these infant formulae.

For an equal energy value the infant formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 2, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2. The ratio of methionine:cystine may be greater than 2 but shall not be greater than 3 provided that the suitability of the product for the particular nutritional use by infants is demonstrated through appropriate studies, performed following generally accepted expert guidance on the design and conduct of such studies.

The L-carnitine content shall be at least equal to 0,3 mg/100 kJ (1,2 mg/100 kcal).

2.4 In all cases, amino acids may be added to infant formulae solely for the purpose of improving the nutritional value of the proteins, and only in the proportions necessary for that purpose.

3. TAURINE

If added to infant formulae, the amount of taurine shall not be greater than 2,9 mg/100 kJ (12 mg/100 kcal).

4. CHOLINE

Minimum	Maximum
1,7 mg/100 kJ (7 mg/100 kcal)	12 mg/100 kJ (50 mg/100 kcal)

5. LIPIDS

Minimum	Maximum
1,05 g/100 kJ (4,4 g/100 kcal)	1,4 g/100 kJ (6,0 g/100 kcal)

5.1 The use of the following substances shall be prohibited:

— sesame seed oil,

— cotton seed oil.

5.2 **Lauric acid and myristic acid**

Minimum	Maximum
—	separately or as a whole: 20 % of the total fat content

5.3 The *trans* fatty acid content shall not exceed 3 % of the total fat content.

5.4 The erucic acid content shall not exceed 1 % of the total fat content.

5.5 **Linoleic acid (in the form of glycerides = linoleates)**

Minimum	Maximum
70 mg/100 kJ (300 mg/100 kcal)	285 mg/100 kJ (1 200 mg/100 kcal)

5.6 The alpha-linolenic acid content shall not be less than 12 mg/100 kJ (50 mg/100 kcal).

The linoleic:alpha-linolenic acid ratio shall not be less than 5 nor greater than 15.

5.7 Long-chain (20 and 22 carbon atoms) polyunsaturated fatty acids (LCP) may be added. In that case their content shall not exceed:

— 1 % of the total fat content for n-3 LCP, and

— 2 % of the total fat content for n-6 LCP (1 % of the total fat content for arachidonic acid (20:4 n-6))

The eicosapentaenoic acid (20:5 n-3) content shall not exceed that of docosahexaenoic (22:6 n-3) acid content.

The docosahexaenoic acid (22:6 n-3) content shall not exceed that of n-6 LCP.

6. PHOSPHOLIPIDS

The amount of phospholipids in infant formulae shall not be greater than 2 g/l.

7. INOSITOL

Minimum	Maximum
1 mg/100 kJ (4 mg/100 kcal)	10 mg/100 kJ (40 mg/100 kcal)

8. CARBOHYDRATES

Minimum	Maximum
2,2 g/100 kJ (9 g/100 kcal)	3,4 g/100 kJ (14 g/100 kcal)

8.1 Only the following carbohydrates may be used:

— lactose,

— maltose,

— sucrose,

— glucose,

— malto-dextrins,

— glucose syrup or dried glucose syrup,

— pre-cooked starch

— gelatinised starch

} naturally free of gluten.

8.2 **Lactose**

Minimum	Maximum
1,1 g/100 kJ	—
(4,5 g/100 kcal)	—

This provision shall not apply to infant formulae in which soya protein isolates represent more than 50 % of the total protein content.

8.3 **Sucrose**

Sucrose may only be added to infant formulae manufactured from protein hydrolysates. If added, the sucrose content shall not exceed 20 % of the total carbohydrate content.

8.4 **Glucose**

Glucose may only be added to infant formulae manufactured from protein hydrolysates. If added, the glucose content shall not exceed 0,5 g/100 kJ (2 g/100 kcal).

8.5 **Pre-cooked starch and/or gelatinised starch**

Minimum	Maximum
—	2 g/100 ml, and 30 % of the total carbohydrate content

9. FRUCTO-OLIGOSACCHARIDES AND GALACTO-OLIGOSACCHARIDES

Fructo-oligosaccharides and galacto-oligosaccharides may be added to infant formulae. In that case their content shall not exceed: 0,8 g/100 ml in a combination of 90 % oligogalactosyl-lactose and 10 % high molecular weight oligofructosyl-saccharose.

Other combinations and maximum levels of fructo-oligosaccharides and galacto-oligosaccharides may be used in accordance with Article 5.

10. MINERAL SUBSTANCES

10.1 **Infant formulae manufactured from cows' milk proteins or protein hydrolysates**

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Sodium (mg)	5	14	20	60
Potassium (mg)	15	38	60	160
Chloride (mg)	12	38	50	160
Calcium (mg)	12	33	50	140
Phosphorus (mg)	6	22	25	90
Magnesium (mg)	1,2	3,6	5	15
Iron (mg)	0,07	0,3	0,3	1,3
Zinc (mg)	0,12	0,36	0,5	1,5
Copper (µg)	8,4	25	35	100

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Iodine (μg)	2,5	12	10	50
Selenium (μg)	0,25	2,2	1	9
Manganese (μg)	0,25	25	1	100
Fluoride (μg)	—	25	—	100

The calcium:phosphorus ratio shall not be less than 1 nor greater than 2.

10.2 **Infant formulae manufactured from soya protein isolates, alone or in a mixture with cows' milk proteins**

All requirements of point 10.1 shall apply, except for those concerning iron and phosphorus, which shall be as follows:

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Iron (mg)	0,12	0,5	0,45	2
Phosphorus (mg)	7,5	25	30	100

11. VITAMINS

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Vitamin A (μg-RE) (1)	14	43	60	180
Vitamin D (μg) (2)	0,25	0,65	1	2,5
Thiamin (μg)	14	72	60	300
Riboflavin (μg)	19	95	80	400
Niacin (μg) (3)	72	375	300	1 500
Pantothenic acid (μg)	95	475	400	2 000
Vitamin B_6 (μg)	9	42	35	175
Biotin (μg)	0,4	1,8	1,5	7,5
Folic Acid (μg)	2,5	12	10	50
Vitamin B_{12} (μg)	0,025	0,12	0,1	0,5
Vitamin C (mg)	2,5	7,5	10	30
Vitamin K (μg)	1	6	4	25
Vitamin E (mg α-TE) (4)	0,5/g of polyunsaturated fatty acids expressed as linoleic acid as corrected for the double bonds (5) but in no case less than 0,1 mg per 100 available kJ	1,2	0,5/g of polyunsaturated fatty acids expressed as linoleic acid as corrected for the double bonds (5) but in no case less than 0,5 mg per 100 available kcal	5

(1) RE = all trans retinol equivalent.
(2) In the form of cholecalciferol, of which 10 μg = 400 i.u. of vitamin D.
(3) Preformed niacin.
(4) α-TE = d-α-tocopherol equivalent.
(5) 0,5 mg α-TE/1 g linoleic acid (18:2 n-6); 0,75 mg α-TE/1 g α-linolenic acid (18:3 n-3); 1,0 mg α-TE/1 g arachidonic acid (20:4 n-6); 1,25 mg α-TE/1 g eicosapentaenoic acid (20:5 n-3); 1,5 mg α-TE/1 g docosahexaenoic acid (22:6 n-3).

12. NUCLEOTIDES

The following nucleotides may be added:

	Maximum [1]	
	(mg/100 kJ)	(mg/100 kcal)
cytidine 5′-monophosphate	0,60	2,50
uridine 5′-monophosphate	0,42	1,75
adenosine 5′-monophosphate	0,36	1,50
guanosine 5′-monophosphate	0,12	0,50
inosine 5′-monophosphate	0,24	1,00

[1] The total concentration of nucleotides shall not exceed 1,2 mg/100 kJ (5 mg/100 kcal).

ANNEX II

ESSENTIAL COMPOSITION OF FOLLOW-ON FORMULAE WHEN RECONSTITUTED AS INSTRUCTED BY THE MANUFACTURER

The values set out in this Annex refer to the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer.

1. ENERGY

Minimum	Maximum
250 kJ/100 ml (60 kcal/100 ml)	295 kJ/100 ml (70 kcal/100 ml)

2. PROTEINS

(Protein content = nitrogen content × 6,25)

2.1 **Follow-on formulae manufactured from cows' milk proteins**

Minimum	Maximum
0,45 g/100 kJ (1,8 g/100 kcal)	0,8 g/100 kJ (3,5 g/100 kcal)

For an equal energy value, the follow-on formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 3, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2.

2.2 **Follow-on formulae manufactured from protein hydrolysates**

Minimum	Maximum
0,56 g/100 kJ (2,25 g/100 kcal)	0,8 g/100 kJ (3,5 g/100 kcal)

For an equal energy value, the follow-on formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 3, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2.

2.3 **Follow-on formulae manufactured from soya protein isolates, alone or in a mixture with cows' milk proteins**

Minimum	Maximum
0,56 g/100 kJ (2,25 g/100 kcal)	0,8 g/100 kJ (3,5 g/100 kcal)

Only protein isolates from soya shall be used in manufacturing these formulae.

For an equal energy value the follow-on formula must contain an available quantity of each indispensable and conditionally indispensable amino acid at least equal to that contained in the reference protein (breast milk, as defined in Annex V). Nevertheless, for calculation purposes, the concentration of methionine and cystine may be added together if the methionine:cystine ratio is not greater than 3, and the concentration of phenylalanine and tyrosine may be added together if the tyrosine:phenylalanine ratio is not greater than 2.

2.4 In all cases, amino acids may be added to follow-on formulae solely for the purpose of improving the nutritional value of the proteins, and only in the proportions necessary for that purpose.

3. TAURINE

If added to follow-on formulae, the amount of taurine shall not be greater than 2,9 mg/100 kJ (12 mg/100 kcal).

4. LIPIDS

Minimum	Maximum
0,96 g/100 kJ (4,0 g/100 kcal)	1,4 g/100 kJ (6,0 g/100 kcal)

4.1 The use of the following substances shall be prohibited:

— sesame seed oil,

— cotton seed oil.

4.2 **Lauric acid and myristic acid**

Minimum	Maximum
—	separately or as a whole: 20 % of the total fat content

4.3. The *trans* fatty acid content shall not exceed 3 % of the total fat content.

4.4 The erucic acid content shall not exceed 1% of the total fat content.

4.5 **Linoleic acid (in the form of glycerides = linoleates)**

Minimum	Maximum
70 mg/100 kJ (300 mg/100 kcal)	285 mg/100 kJ (1 200 mg/100 kcal)

4.6 The alpha-linolenic acid content shall not be less than 12 mg/100 kJ (50 mg/100 kcal).

The linoleic:alpha-linolenic acid ratio shall not be less than 5 nor greater than 15.

4.7 Long-chain (20 and 22 carbon atoms) polyunsaturated fatty acids (LCP) may be added. In that case their content shall not exceed:

— 1 % of the total fat content for n-3 LCP, and

— 2 % of the total fat content for n-6 LCP (1 % of the total fat content for arachidonic acid (20:4 n-6))

The eicosapentaenoic acid (20:5 n-3) content shall not exceed that of docosahexaenoic (22:6 n-3) acid content.

The docosahexaenoic (22:6 n-3) acid content shall not exceed that of n-6 LCP.

5. PHOSPHOLIPIDS

The amount of phospholipids in follow-on formulae shall not be greater than 2 g/l.

6. CARBOHYDRATES

Minimum	Maximum
2,2 g/100 kJ (9 g/100 kcal)	3,4 g/100 kJ (14 g/100 kcal)

6.1 The use of ingredients containing gluten shall be prohibited.

6.2 **Lactose**

Minimum	Maximum
1,1 g/100 kJ (4,5 g/100 kcal)	—

This provision shall not apply to follow-on formulae in which soya protein isolates represent more than 50 % of the total protein content.

6.3 **Sucrose, fructose, honey**

Minimum	Maximum
—	separately or as a whole: 20 % of the total carbohydrate content

Honey shall be treated to destroy spores of *Clostridium botulinum*.

6.4 **Glucose**

Glucose may only be added to follow-on formulae manufactured from protein hydrolysates. If added, the glucose content shall not exceed 0,5 g/100 kJ (2 g/100 kcal).

7. FRUCTO-OLIGOSACCHARIDES AND GALACTO-OLIGOSACCHARIDES

Fructo-oligosaccharides and galacto-oligosaccharides may be added to follow-on formulae. In that case their content shall not exceed: 0,8 g/100 ml in a combination of 90 % oligogalactosyl-lactose and 10 % high molecular weight oligofructosyl-saccharose.

Other combinations and maximum levels of fructo-oligosaccharides and galacto-oligosaccharides may be used in accordance with Article 6.

8. MINERAL SUBSTANCES

8.1 **Follow-on formulae manufactured from cows' milk proteins or protein hydrolysates**

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Sodium (mg)	5	14	20	60
Potassium (mg)	15	38	60	160
Chloride (mg)	12	38	50	160
Calcium (mg)	12	33	50	140
Phosphorus (mg)	6	22	25	90
Magnesium (mg)	1,2	3,6	5	15
Iron (mg)	0,14	0,5	0,6	2
Zinc (mg)	0,12	0,36	0,5	1,5
Copper (μg)	8,4	25	35	100
Iodine (μg)	2,5	12	10	50
Selenium (μg)	0,25	2,2	1	9
Manganese (μg)	0,25	25	1	100
Fluoride (μg)	—	25	—	100

The calcium:phosphorus ratio in follow-on formulae shall not be less than 1,0 nor greater than 2,0.

8.2 **Follow-on formulae manufactured from soya protein isolates, alone or in a mixture with cows' milk proteins**

All requirements of point 8.1 shall apply, except for those concerning iron, and phosphorus, which shall be as follows:

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Iron (mg)	0,22	0,65	0,9	2,5
Phosphorus (mg)	7,5	25	30	100

9. VITAMINS

	Per 100 kJ		Per 100 kcal	
	Minimum	Maximum	Minimum	Maximum
Vitamin A (µg-RE) (1)	14	43	60	180
Vitamin D (µg) (2)	0,25	0,75	1	3
Thiamin (µg)	14	72	60	300
Riboflavin (µg)	19	95	80	400
Niacin (µg) (3)	72	375	300	1 500
Pantothenic acid (µg)	95	475	400	2 000
Vitamin B_6 (µg)	9	42	35	175
Biotin (µg)	0,4	1,8	1,5	7,5
Folic Acid (µg)	2,5	12	10	50
Vitamin B_{12} (µg)	0,025	0,12	0,1	0,5
Vitamin C (mg)	2,5	7,5	10	30
Vitamin K (µg)	1	6	4	25
Vitamin E (mg α-TE) (4)	0,5/g poly-unsaturated fatty acids expressed as linoleic acid as corrected for the double bonds (5) but in no case less than 0,1 mg per 100 available kJ	1,2	0,5/g poly-unsaturated fatty acids expressed as linoleic acid as corrected for the double bonds (5) but in no case less than 0,5 mg per 100 available kcal	5

(1) RE = all *trans* retinol equivalent.
(2) In the form of cholecalciferol, of which10 µg = 400 i.u. of vitamin D.
(3) Preformed niacin.
(4) α-TE = d-α-tocopherol equivalent.
(5) 0,5 mg α-TE/1 g linoleic acid (18:2 n-6); 0,75 mg α-TE/1 g α-linolenic acid (18:3 n-3); 1,0 mg α-TE/1 g arachidonic acid (20:4 n-6); 1,25 mg α-TE/1 g eicosapentaenoic acid (20:5 n-3); 1,5 mg α-TE/1 g docosahexaenoic acid (22:6 n-3).

10. NUCLEOTIDES

The following nucleotides may be added:

	Maximum (1)	
	(mg/100 kJ)	(mg/100 kcal)
cytidine 5′-monophosphate	0,60	2,50
uridine 5′-monophosphate	0,42	1,75
adenosine 5′-monophosphate	0,36	1,50
guanosine 5′-monophosphate	0,12	0,50
inosine 5′-monophosphate	0,24	1,00

(1) The total concentration of nucleotides shall not exceed 1,2 mg/100 kJ (5 mg/100 kcal).

ANNEX III

NUTRITIONAL SUBSTANCES

1. **Vitamins**

Vitamin	Vitamin formulation
Vitamin A	Retinyl acetate
	Retinyl palmitate
	Retinol
Vitamin D	Vitamin D_2 (ergocalciferol)
	Vitamin D_3 (cholecalciferol)
Vitamin B_1	Thiamin hydrochloride
	Thiamin mononitrate
Vitamin B_2	Riboflavin
	Riboflavin-5′-phosphate, sodium
Niacin	Nicotinamide
	Nicotinic acid
Vitamin B_6	Pyridoxine hydrochloride
	Pyridoxine-5′-phosphate
Folate	Folic acid
Pantothenic acid	D-pantothenate, calcium
	D-pantothenate, sodium
	Dexpanthenol
Vitamin B_{12}	Cyanocobalamin
	Hydroxocobalamin
Biotin	D-biotin
Vitamin C	L-ascorbic acid
	Sodium L-ascorbate
	Calcium L-ascorbate
	6-palmityl-L-ascorbic acid (ascorbyl palmitate)
	Potassium ascorbate
Vitamin E	D-alpha tocopherol
	DL-alpha tocopherol
	D-alpha tocopherol acetate
	DL-alpha tocopherol acetate
Vitamin K	Phylloquinone (Phytomenadione)

2. **Mineral substances**

Mineral substances	Permitted salts
Calcium (Ca)	Calcium carbonate
	Calcium chloride
	Calcium salts of citric acid
	Calcium gluconate
	Calcium glycerophosphate
	Calcium lactate
	Calcium salts of orthophosphoric acid
	Calcium hydroxide
Magnesium (Mg)	Magnesium carbonate
	Magnesium chloride
	Magnesium oxide
	Magnesium salts of orthophosphoric acid
	Magnesium sulphate
	Magnesium gluconate
	Magnesium hydroxide
	Magnesium salts of citric acid
Iron (Fe)	Ferrous citrate
	Ferrous gluconate
	Ferrous lactate
	Ferrous sulphate
	Ferric ammonium citrate
	Ferrous fumarate
	Ferric diphosphate (Ferric pyrophosphate)
	Ferrous bisglycinate
Copper (Cu)	Cupric citrate
	Cupric gluconate
	Cupric sulphate
	Copper-lysine complex
	Cupric carbonate
Iodine (I)	Potassium iodide
	Sodium iodide
	Potassium iodate
Zinc (Zn)	Zinc acetate
	Zinc chloride
	Zinc lactate
	Zinc sulphate
	Zinc citrate
	Zinc gluconate
	Zinc oxide

Mineral substances	Permitted salts
Manganese (Mn)	Manganese carbonate
	Manganese chloride
	Manganese citrate
	Manganese sulphate
	Manganese gluconate
Sodium (Na)	Sodium bicarbonate
	Sodium chloride
	Sodium citrate
	Sodium gluconate
	Sodium carbonate
	Sodium lactate
	Sodium salts of orthophosphoric acid
	Sodium hydroxide
Potassium (K)	Potassium bicarbonate
	Potassium carbonate
	Potassium chloride
	Potassium salts of citric acid
	Potassium gluconate
	Potassium lactate
	Potassium salts of orthophosphoric acid
	Potassium hydroxide
Selenium (Se)	Sodium selenate
	Sodium selenite

3. **Amino acids and other nitrogen compounds**

L-cystine and its hydrochloride
L-histidine and its hydrochloride
L-isoleucine and its hydrochloride
L-leucine and its hydrochloride
L-lysine and its hydrochloride
L-cysteine and its hydrochloride
L-methionine
L-phenylalanine
L-threonine
L-tryptophan
L-tyrosine
L-valine
L-carnitine and its hydrochloride
L-carnitine-L-tartrate
Taurine

Cytidine 5′-monophosphate and its sodium salt
Uridine 5′-monophosphate and its sodium salt
Adenosine 5′-monophosphate and its sodium salt
Guanosine 5′-monophosphate and its sodium salt
Inosine 5′-monophosphate and its sodium salt

4. **Other nutritional substances**

Choline
Choline chloride
Choline citrate
Choline bitartrate
Inositol

ANNEX IV

NUTRITION AND HEALTH CLAIMS FOR INFANT FORMULAE AND CONDITIONS WARRANTING A CORRESPONDING CLAIM

1. NUTRITION CLAIMS

Nutrition claim related to	Conditions warranting the nutrition claim
1.1 Lactose only	Lactose is the only carbohydrate present.
1.2 Lactose free	Lactose content is not greater than 2,5 mg/100 kJ (10 mg/100 kcal).
1.3 Added LCP or an equivalent nutrition claim related to the addition of docosahexaenoic acid	The docosahexaenoic acid content is not less than 0,2 % of the total fatty acid content.
1.4 Nutrition claims on the addition of the following optional ingredients:	
1.4.1 taurine	Voluntarily added at a level that would be appropriate for the intended particular use by infants and in accordance with the conditions set out in Annex I.
1.4.2 fructo-oligosaccharides and galacto-oligosaccharides	
1.4.3 nucleotides	

2. HEALTH CLAIMS (INCLUDING REDUCTION OF DISEASE RISK CLAIMS)

Nutrition claim related to	Conditions warranting the health claim
2.1 Reduction of risk to allergy to milk proteins. This health claim may include terms referring to reduced allergen or reduced antigen properties.	(a) Objective and scientifically verified data as proof to the claimed properties must be available; (b) The infant formulae shall satisfy the provisions set out in point 2.2 of Annex I and the amount of immunoreactive protein measured with methods generally acceptable as appropriate shall be less than 1 % of nitrogen containing substances in the formulae; (c) The label shall indicate that the product must not be consumed by infants allergic to the intact proteins from which it is manufactured unless generally accepted clinical tests provide proof of the infant formulae's tolerance in more than 90 % of infants (confidence interval 95 %) hypersensitive to proteins from which the hydrolysate is manufactured; (d) The infant formulae administered orally must not induce sensitisation, in animals, to the intact proteins from which the infant formulae are manufactured.

ANNEX V

INDISPENSABLE AND CONDITIONALLY INDISPENSABLE AMINO ACIDS IN BREAST MILK

For the purpose of this Directive, the indispensable and conditionally indispensable amino acids in breast milk, expressed in mg per 100 kJ and 100 kcal, are the following:

	Per 100 kJ [1]	Per 100 kcal
Cystine	9	38
Histidine	10	40
Isoleucine	22	90
Leucine	40	166
Lysine	27	113
Methionine	5	23
Phenylalanine	20	83
Threonine	18	77
Tryptophan	8	32
Tyrosine	18	76
Valine	21	88

[1] 1 kJ = 0,239 kcal.

ANNEX VI

Specification for the protein content and source and the processing of protein used in the manufacture of infant formulae with a protein content less than 0,56 g/100 kJ (2,25 g/100 kcal) manufactured from hydrolysates of whey proteins derived from cows' milk protein

1. **Protein content**

Protein content = nitrogen content × 6,25

Minimum	Maximum
0,44 g/100 kJ	0,7 g/100 kJ
(1,86 g/100 kcal)	(3 g/100 kcal)

2. **Protein source**

Demineralised sweet whey protein derived from cows' milk after enzymatic precipitation of caseins using chymosin, consisting of:

(a) 63 % caseino-glycomacropeptide free whey protein isolate with a minimum protein content of 95 % of dry matter and protein denaturation of less than 70 % and a maximum ash content of 3 %; and

(b) 37 % sweet whey protein concentrate with a minimum protein content of 87 % of dry matter and protein denaturation of less than 70 % and a maximum ash content of 3,5 %.

3. **Protein processing**

Two-stage hydrolysis process using a trypsin preparation with a heat-treatment step (from 3 to 10 minutes at 80 to 100 °C) between the two hydrolysis steps.

ANNEX VII

REFERENCE VALUES FOR NUTRITION LABELLING FOR FOODS INTENDED FOR INFANTS AND YOUNG CHILDREN

Nutrient	Labelling reference value
Vitamin A	(µg) 400
Vitamin D	(µg) 7
Vitamin E	(mg TE) 5
Vitamin K	(µg) 12
Vitamin C	(mg) 45
Thiamin	(mg) 0,5
Riboflavin	(mg) 0,7
Niacin	(mg) 7
Vitamin B_6	(mg) 0,7
Folate	(µg) 125
Vitamin B_{12}	(µg) 0,8
Pantothenic acid	(mg) 3
Biotin	(µg) 10
Calcium	(mg) 550
Phosphorus	(mg) 550
Potassium	(mg) 1 000
Sodium	(mg) 400
Chloride	(mg) 500
Iron	(mg) 8
Zinc	(mg) 5
Iodine	(µg) 80
Selenium	(µg) 20
Copper	(mg) 0,5
Magnesium	(mg) 80
Manganese	(mg) 1,2

ANNEX VIII

PESTICIDES WHICH SHALL NOT BE USED IN AGRICULTURAL PRODUCTION INTENDED FOR THE PRODUCTION OF INFANT FORMULAE AND FOLLOW ON FORMULAE

Table 1

Chemical name of the substance (residue definition)
Disulfoton (sum of disulfoton, disulfoton sulfoxide and disulfoton sulfone expressed as disulfoton)
Fensulfothion (sum of fensulfothion, its oxygen analogue and their sulfones, expressed as fensulfothion)
Fentin, expressed as triphenyltin cation
Haloxyfop (sum of haloxyfop, its salts and esters including conjugates, expressed as haloxyfop)
Heptachlor and *trans*-heptachlor epoxide, expressed as heptachlor
Hexachlorobenzene
Nitrofen
Omethoate
Terbufos (sum of terbufos, its sulfoxide and sulfone, expressed as terbufos)

Table 2

Chemical name of the substance
Aldrin and dieldrin, expressed as dieldrin
Endrin

ANNEX IX

SPECIFIC MAXIMUM RESIDUE LEVELS OF PESTICIDES OR METABOLITES OF PESTICIDES IN INFANT FORMULAE AND FOLLOW-ON FORMULAE

Chemical name of the substance	Maximum residue level (mg/kg)
Cadusafos	0,006
Demeton-S-methyl/demeton-S-methyl sulfone/oxydemeton-methyl (individually or combined, expressed as demeton-S-methyl)	0,006
Ethoprophos	0,008
Fipronil (sum of fipronil and fipronil-desulfinyl, expressed as fipronil)	0,004
Propineb/propylenethiourea (sum of propineb and propylenethiourea)	0,006

ANNEX X

PART A

Repealed Directive, with list of its successive amendments

(referred to in Article 19)

Commission Directive 91/321/EEC (OJ L 175, 4.7.1991, p. 35).

Point XI.C.IX.5 of Annex I to the 1994 Act of Accession, p. 212.

Commission Directive 96/4/EC (OJ L 49, 28.2.1996, p. 12).

Commission Directive 1999/50/EC (OJ L 139, 2.6.1999, p. 29).

Commission Directive 2003/14/EC (OJ L 41, 14.2.2003, p. 37).

Point 1.J.3 of Annex II to the 2003 Act of Accession, p. 93.

PART B

List of time limits for transposition into national law

(referred to in Article 19)

Directive	Time limit for transposition	Permission of trade in products complying with this Directive	Prohibition of trade in products not complying with this Directive
91/321/EEC		1 December 1992	1 June 1994
96/4/EC	31 March 1997	1 April 1997	31 March 1999
1999/50/EC	30 June 2000	30 June 2000	1 July 2002
2003/14/EC	6 March 2004	6 March 2004	6 March 2005

ANNEX XI

CORRELATION TABLE

Directive 91/321/EEC	This Directive
Article 1(1)	Article 1
Article 1(2)	Article 2
Article 2	Article 3
Article 3(1)	Article 5
Article 3(2)	Article 6
Article 3(3)	Article 7(4)
Article 4	Article 7(1) to (3)
Article 5(1), first subparagraph	Article 8(1)
Article 5(1), second subparagraph	Article 8(2) and (3)
Article 5(2)	—
—	Article 9
Article 6(1), first sentence	Article 4
Article 6(1), second sentence	—
Article 6(2)	Article 10(1)
Article 6(3)(a), introductory phrase	Article 10(2), introductory phrase
Article 6(3)(a)(i)	Article 10(2)(a)
Article 6(3)(a)(ii)	Article 10(2)(b)
Article 6(3)(b), first subparagraph	Article 10(3)
Article 6(3)(b), second subparagraph	—
Article 6(3)(c)	Article 10(4)
Article 6(4)	—
Article 7(1), first subparagraph	Article 11
Article 7(1), second subparagraph	Article 12
Article 7(2)(a)	Article 13(1)(a)
Article 7(2)(b)	—
Article 7(2)(c)	Article 13(1)(b)
Article 7(2)(d)	Article 13(1)(c)

Directive 91/321/EEC	This Directive
Article 7(2)(e)	Article 13(1)(d)
Article 7(2)(f)	Article 13(1)(e)
Article 7(2a)	Article 13(2)
Article 7(3)	Article 13(3)
Article 7(4)	Article 13(4)
Article 7(5)	Article 13(5)
Article 7(6)	Article 13(6)
—	Article 13(7)
Article 7(7)	Article 13(8)
Article 8	Article 14
Article 9	Article 15
Article 10	—
—	Article 16
—	Article 17
—	Article 18
—	Article 19
—	Article 20
Article 11	Article 21
Annexes I to V	Annexes I to V
Annex VI	—
Annex VII	—
—	Annex VI
Annexes VIII to X	Annexes VII to IX
—	Annex X
—	Annex XI

Article 25

Specific rules on disease prevention and veterinary treatment in beekeeping

1. For the purposes of protecting frames, hives and combs, in particular from pests, only rodenticides (to be used only in traps), and appropriate products listed in Annex II, are permitted.

2. Physical treatments for disinfection of apiaries such as steam or direct flame are permitted.

3. The practice of destroying the male brood is permitted only to isolate the infestation of *Varroa destructor*.

4. If despite all preventive measures, the colonies become sick or infested, they shall be treated immediately and, if necessary, the colonies can be placed in isolation apiaries.

5. Veterinary medicinal products may be used in organic beekeeping in so far as the corresponding use is authorised in the Member State in accordance with the relevant Community provisions or national provisions in conformity with Community law.

6. Formic acid, lactic acid, acetic acid and oxalic acid as well as menthol, thymol, eucalyptol or camphor may be used in cases of infestation with *Varroa destructor*.

7. If a treatment is applied with chemically synthesised allopathic products, during such a period, the colonies treated shall be placed in isolation apiaries and all the wax shall be replaced with wax coming from organic beekeeping. Subsequently, the conversion period of one year laid down in Article 38(3) will apply to those colonies.

8. The requirements laid down in paragraph 7 shall not apply to products listed in paragraph 6.

CHAPTER 3

Processed products

Article 26

Rules for the production of processed feed and food

1. Additives, processing aids and other substances and ingredients used for processing food or feed and any processing practice applied, such as smoking, shall respect the principles of good manufacturing practice.

2. Operators producing processed feed or food shall establish and update appropriate procedures based on a systematic identification of critical processing steps.

3. The application of the procedures referred to in paragraph 2 shall guarantee at all times that the produced processed products comply with the organic production rules.

4. Operators shall comply with and implement the procedures referred to in paragraph 2. In particular, operators shall:

(a) take precautionary measures to avoid the risk of contamination by unauthorised substances or products;

(b) implement suitable cleaning measures, monitor their effectiveness and record these operations;

(c) guarantee that non-organic products are not placed on the market with an indication referring to the organic production method.

5. Further to the provisions laid down in paragraphs 2 and 4, when non-organic products are also prepared or stored in the preparation unit concerned, the operator shall:

(a) carry out the operations continuously until the complete run has been dealt with, separated by place or time from similar operations performed on non-organic products;

(b) store organic products, before and after the operations, separate by place or time from non-organic products;

(c) inform the control authority or control body thereof and keep available an updated register of all operations and quantities processed;

(d) take the necessary measures to ensure identification of lots and to avoid mixtures or exchanges with non-organic products;

(e) carry out operations on organic products only after suitable cleaning of the production equipment.

Article 27

Use of certain products and substances in processing of food

1. For the purpose of Article 19(2)(b) of Regulation (EC) No 834/2007, only the following substances can be used in the processing of organic food, with the exception of wine:

(a) substances listed in Annex VIII to this Regulation;

(b) preparations of micro-organisms and enzymes normally used in food processing;

(c) substances, and products as defined in Articles 1(2)(b)(i) and 1(2)(c) of Council Directive 88/388/EEC ([14]) labelled as natural flavouring substances or natural flavouring preparations, according to Articles 9(1)(d) and (2) of that Directive.

(d) colours for stamping meat and eggshells in accordance with, respectively, Article 2(8) and Article 2(9) of European Parliament and Council Directive 94/36/EC ([15]);

(e) drinking water and salt (with sodium chloride or potassium chloride as basic components) generally used in food processing;

(f) minerals (trace elements included), vitamins, aminoacids, and micronutrients, only authorised as far their use is legally required in the foodstuffs in which they are incorporated.

2. For the purpose of the calculation referred to in Article 23 (4)(a)(ii) of Regulation (EC) No 834/2007,

(a) food additives listed in Annex VIII and marked with an asterisk in the column of the additive code number, shall be calculated as ingredients of agricultural origin;

(b) preparations and substances referred to in paragraph (1)(b), (c),(d),(e) and (f) of this Article and substances not marked with an asterisk in the column of the additive code number shall not be calculated as ingredients of agricultural origin.

3. The use of the following substances listed in Annex VIII shall be re-examined before 31 December 2010:

(a) Sodium nitrite and potassium nitrate in Section A with a view to withdrawing these additives;

(b) Sulphur dioxide and potassium metabisulphite in Section A;

(c) Hydrochloric acid in Section B for the processing of Gouda, Edam and Maasdammer cheeses, Boerenkaas, Friese, and Leidse Nagelkaas.

The re-examination referred to in point (a) shall take account of the efforts made by Member States to find safe alternatives to nitrites/nitrates and in establishing educational programmes in alternative processing methods and hygiene for organic meat processors/manufacturers.

([14]) OJ L 184, 15.7.1988, p. 61.
([15]) OJ L 237, 10.9.1994, p. 13.

Article 28

Use of certain non-organic ingredients of agricultural origin in processing food

For the purpose of Article 19(2)(c) of Regulation (EC) No 834/2007, non-organic agricultural ingredients listed in Annex IX to this Regulation can be used in the processing of organic food.

Article 29

Authorisation of non-organic food ingredients of agricultural origin by Member State

1. Where an ingredient of agricultural origin is not included in Annex IX to this Regulation, that ingredient may only be used under the following conditions:

(a) the operator has notified to the competent authority of the Member State all the requisite evidence showing that the ingredient concerned is not produced in sufficient quantity in the Community in accordance with the organic production rules or cannot be imported from third countries;

(b) the competent authority of the Member State has provisionally authorised, the use for a maximum period of 12 months after having verified that the operator has undertaken the necessary contacts with suppliers in the Community to ensure himself of the unavailability of the ingredients concerned with the required quality requirements;

(c) no decision has been taken, in accordance with the provisions of paragraphs 3 or 4 that a granted authorisation with regard to the ingredient concerned shall be withdrawn.

The Member State may prolong the authorisation provided for in point (b) a maximum of three times for 12 months each.

2. Where an authorisation as referred to in paragraph 1 has been granted, the Member State shall immediately notify to the other Member States and to the Commission, the following information:

(a) the date of the authorisation and in case of a prolonged authorisation, the date of the first authorisation;

(b) the name, address, telephone, and where relevant, fax and e-mail of the holder of the authorisation; the name and address of the contact point of the authority which granted the authorisation;

(c) the name and, where necessary, the precise description and quality requirements of the ingredient of agricultural origin concerned;

Appendix D. Relevant FDA Regulations:

21 CFR 107.100 Nutrient specifications (for infant formula)

21 CFR 182.8250 Choline bitartrate

21 CFR 182.8252 Choline chloride

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.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6760 Sodium hexametaphosphate.

(a) *Product.* Sodium hexametaphosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6769 Sodium metaphosphate.

(a) *Product.* Sodium metaphosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6778 Sodium phosphate.

(a) *Product.* Sodium phosphate (mono-, di-, and tribasic).

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6787 Sodium pyrophosphate.

(a) *Product.* Sodium pyrophosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6789 Tetra sodium pyrophosphate.

(a) *Product.* Tetra sodium pyrophosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.6810 Sodium tripolyphosphate.

(a) *Product.* Sodium tripolyphosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

Subpart H—Stabilizers

§ 182.7255 Chondrus extract.

(a) *Product.* Chondrus extract (carrageenin).

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

Subpart I—Nutrients

SOURCE: 45 FR 58838, Sept. 5, 1980, unless otherwise noted.

§ 182.8013 Ascorbic acid.

(a) *Product.* Ascorbic acid.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8159 Biotin.

(a) *Product.* Biotin.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8217 Calcium phosphate.

(a) *Product.* Calcium phosphate (mono-, di-, and tribasic).

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8223 Calcium pyrophosphate.

(a) *Product.* Calcium pyrophosphate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8250 Choline bitartrate.

(a) *Product.* Choline bitartrate.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8252 Choline chloride.

(a) *Product.* Choline chloride.

(b) *Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.

§ 182.8778 Sodium phosphate.

(a) *Product.* Sodium phosphate (mono-, di-, and tribasic).

(b) *Conditions of use.* This substance is generally recognized as safe when

Appendix E. Food Chemicals Codex monograph for choline bitartrate.

Food Chemicals Codex monograph for choline chloride

JECFA Evaluation of Choline Salts.

prepared aqua regia, and dilute with water to a volume, in mL, equivalent to the weight, in g, of the initial sample. One mL of the final dilution is equivalent to 1 g of sample.

Sample solution: Transfer 2.0 mL of the *Sample stock solution* to a 50-mL beaker and add 10 mL of water, 1 mL of 1 : 5 sulfuric acid, and 1 mL of a 40 mg/mL potassium permanganate solution. Cover the beaker with a watch glass, boil for a few seconds, and cool.

Acceptance criterion: NMT 1 mg/kg

SPECIFIC TESTS

- **MOISTURE**

Analysis: Determine by ASTM Method E 410-92, *"Moisture and Residue in Liquid Chlorine."*

[NOTE: Retain the residue obtained for use in tests for *Lead* and *Mercury* (above).]

Acceptance criterion: NMT 0.015%, by weight

- **RESIDUE**

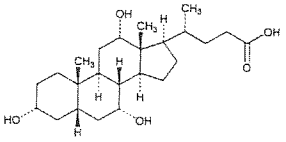
Analysis: Determine by ASTM Method E 410-92, *"Moisture and Residue in Liquid Chlorine."*

[NOTE: Retain the residue obtained for use in tests for *Lead* and *Mercury* (above).]

Acceptance criterion: NMT 0.015%, by weight, of nonvolatile matter

Cholic Acid

Cholalic Acid
3,7,12-Trihydroxycholanic Acid



$C_{24}H_{40}O_5$ Formula wt 408.58

INS: 1000 CAS: [81-25-4]

DESCRIPTION

Cholic Acid occurs as colorless plates or as a white, crystalline powder. One g dissolves in about 30 mL of alcohol or acetone and in about 7 mL of glacial acetic acid. It is very slightly soluble in water.

Function Emulsifier

Packaging and Storage Store in tight containers.

IDENTIFICATION

- **PROCEDURE**

Sample solution: 0.2 mg/mL in 50% acetic acid

Analysis: To 1 mL of the *Sample solution*, add 1 mL of a 1 : 100 furfural solution. Cool in an ice bath for 5 min, add 15 mL of 1 : 2 sulfuric acid, mix, and warm in a water bath at 70° for 10 min. Immediately cool in an ice bath, and stir for 2 min.

Acceptance criterion: A blue color appears.

ASSAY

- **PROCEDURE**

Sample: 400 mg

Analysis: Transfer the *Sample* into a 250-mL Erlenmeyer flask, add 20 mL of water and 40 mL of alcohol, cover with a watch glass, heat gently on a steam bath until dissolved, and cool. Add 5 drops of phenolphthalein TS and, using a 10-mL microburet, titrate with 0.1 N sodium hydroxide to the first pink color that persists for 15 s. Perform a blank determination (see *General Provisions*), and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 40.86 mg of $C_{24}H_{40}O_5$.

Acceptance criterion: NLT 98.0% of $C_{24}H_{40}O_5$, calculated on the dried basis

IMPURITIES

Inorganic Impurities

- **LEAD,** *Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method,* Appendix IIIB

Sample: 10 g

Acceptance criterion: NMT 4 mg/kg

SPECIFIC TESTS

- **LOSS ON DRYING,** Appendix IIC (140° under a vacuum of NMT 5 mm Hg, for 4 h)

Acceptance criterion: NMT 0.5%

- **MELTING RANGE OR TEMPERATURE,** Appendix IIB

Acceptance criterion: Between 197° and 202°

- **OPTICAL (SPECIFIC) ROTATION,** Appendix IIB

Sample solution: 20 mg/mL in alcohol

Acceptance criterion: $[\alpha]_D^{25}$ NLT +37°, calculated on the dried basis

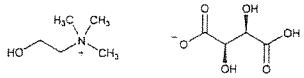
- **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC

Sample: 2 g

Acceptance criterion: NMT 0.1%

Choline Bitartrate

(2-Hydroxyethyl)trimethylammonium-L-(+)-tartrate Salt



$C_9H_{19}NO_7$ Formula wt 253.25

INS: 1001 (v) CAS: [87-67-2]

DESCRIPTION

Choline Bitartrate occurs as a white, hygroscopic, crystalline powder. It is freely soluble in water, slightly soluble in alcohol, and insoluble in ether and in chloroform.

Function Nutrient

Packaging and Storage Store in tight containers.

IDENTIFICATION

- **A. PROCEDURE**
  Sample: 500 mg
  Analysis: Dissolve the *Sample* in 2 mL of water, add 3 mL of 1 N sodium hydroxide, and heat to boiling.
  Acceptance criterion: The odor of trimethylamine is detectable.
- **B. PROCEDURE**
  Sample: 500 mg
  Analysis: Dissolve the *Sample* in 2 mL of iodine TS. A red-brown precipitate forms immediately. Add 5 mL of 1 N sodium hydroxide. The precipitate dissolves, and the solution becomes clear yellow. Heat the solution.
  Acceptance criterion: A pale yellow precipitate forms following the heating step.
- **C. PROCEDURE**
  Sample solution: 10 mg/mL
  Analysis: Add 1 mL of the *Sample solution* and 2 mL of a 20 mg/mL solution of potassium ferrocyanide to 2 mL of cobaltous chloride TS.
  Acceptance criterion: An emerald green color develops immediately.

ASSAY

- **PROCEDURE**
  Sample: 500 mg
  Analysis: Transfer the *Sample* into a 250-mL Erlenmeyer flask. Add 50 mL of glacial acetic acid and warm on a steam bath until dissolution is complete. Cool, add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid to a green endpoint. [CAUTION: Handle perchloric acid in an appropriate fume hood.] Perform a blank determination (see *General Provisions*), and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 25.36 mg of $C_9H_{19}NO_7$.
  Acceptance criterion: NLT 98.0% of $C_9H_{19}NO_7$, calculated on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **LEAD,** *Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method,* Appendix IIIB
  Sample: 5 g
  Acceptance criterion: NMT 2 mg/kg

Organic Impurities

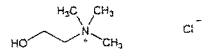
- **1,4-DIOXANE,** Appendix IIIB
  Acceptance criterion: Passes test.

SPECIFIC TESTS

- **OPTICAL (SPECIFIC) ROTATION,** Appendix IIB
  Sample solution: 400 mg/mL
  Acceptance criterion: $[\alpha]_D^{25}$ Between 17.5° and 18.5°
- **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC
  Sample: 2 g
  Acceptance criterion: NMT 0.1%
- **WATER,** *Water Determination,* Appendix IIB
  Sample solution: 2 g of sample in 50 mL of methanol
  [NOTE: Alternatively, the *Water Determination* can be made by drying the sample in a vacuum desiccator over phosphorus pentoxide for 4 h.]
  Acceptance criterion: NMT 0.5%

Choline Chloride

(2-Hydroxyethyl)trimethylammonium Chloride



$C_5H_{14}ClNO$ Formula wt 139.65

INS: 1001(iii) CAS: [67-48-1]

DESCRIPTION

Choline Chloride occurs as colorless or white crystals or as a crystalline powder. It is hygroscopic, and is very soluble in water and in alcohol.

Function Nutrient

Packaging and Storage Store in tight containers.

IDENTIFICATION

- **A. CHLORIDE,** Appendix IIIA
  Sample solution: 50 mg/mL
  Acceptance criterion: Passes tests.
- **B. PROCEDURE**
  Sample: 500 mg
  Analysis: Dissolve the *Sample* in 2 mL of water, add 3 mL of 1 N sodium hydroxide, and heat to boiling.
  Acceptance criterion: The odor of trimethylamine is detectable.
- **C. PROCEDURE**
  Sample: 500 mg
  Analysis: Dissolve the *Sample* in 2 mL of iodine TS. A red-brown precipitate forms immediately. Add 5 mL of 1 N sodium hydroxide. The precipitate dissolves, and the solution becomes clear yellow. Heat the solution.
  Acceptance criterion: A pale yellow precipitate forms following the heating step.
- **D. PROCEDURE**
  Sample solution: 10 mg/mL
  Analysis: Add 1 mL of the *Sample solution* and 2 mL of a 20 mg/mL solution of potassium ferrocyanide to 2 mL of cobaltous chloride TS.
  Acceptance criterion: An emerald green color develops immediately.

ASSAY

- **PROCEDURE**
  Sample: 300 mg
  Analysis: Transfer the *Sample* into a 250-mL Erlenmeyer flask. Add 50 mL of glacial acetic acid and warm on a steam bath until dissolution is complete. Cool, add 10 mL of mercuric acetate and 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid to a green endpoint. [CAUTION: Handle perchloric acid in an appropriate fume hood.] Perform a blank determination (see *General Provisions*), and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 13.96 mg of $C_5H_{14}ClNO$.
  Acceptance criteria: NLT 98.0% and NMT 100.5% of $C_5H_{14}ClNO$, calculated on the anhydrous basis

SIXTH EDITION

FOOD CHEMICALS CODEX

FCC 6

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THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

IDENTIFICATION

• **A. PROCEDURE**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 2 mL of water, add 3 mL of 1 N sodium hydroxide, and heat to boiling.

Acceptance criterion: The odor of trimethylamine is detectable.

• **B. PROCEDURE**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 2 mL of iodine TS. A red-brown precipitate forms immediately. Add 5 mL of 1 N sodium hydroxide. The precipitate dissolves, and the solution becomes clear yellow. Heat the solution.

Acceptance criterion: A pale yellow precipitate forms following the heating step.

• **C. PROCEDURE**

Sample solution: 10 mg/mL

Analysis: Add 1 mL of the *Sample solution* and 2 mL of a 20 mg/mL solution of potassium ferrocyanide to 2 mL of cobaltous chloride TS.

Acceptance criterion: An emerald green color develops immediately.

ASSAY

• **PROCEDURE**

Sample: 500 mg

Analysis: Transfer the *Sample* into a 250-mL Erlenmeyer flask. Add 50 mL of glacial acetic acid and warm on a steam bath until dissolution is complete. Cool, add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid to a green endpoint. [**CAUTION:** Handle perchloric acid in an appropriate fume hood.] Perform a blank determination (see *General Provisions*), and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 25.36 mg of $C_9H_{19}NO_7$.

Acceptance criterion: NLT 98.0% of $C_9H_{19}NO_7$, calculated on the anhydrous basis

IMPURITIES

Inorganic Impurities

• **LEAD,** *Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method,* Appendix IIIB

Sample: 5 g

Acceptance criterion: NMT 2 mg/kg

Organic Impurities

• **1,4-DIOXANE,** Appendix IIIB

Acceptance criterion: Passes test.

SPECIFIC TESTS

• **OPTICAL (SPECIFIC) ROTATION,** Appendix IIB

Sample solution: 400 mg/mL

Acceptance criterion: $[\alpha]_D^{25}$ Between 17.5° and 18.5°

• **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC

Sample: 2 g

Acceptance criterion: NMT 0.1%

• **WATER,** *Water Determination,* Appendix IIB

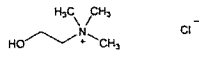
Sample solution: 2 g of sample in 50 mL of methanol

[NOTE: Alternatively, the *Water Determination* can be made by drying the sample in a vacuum desiccator over phosphorus pentoxide for 4 h.]

Acceptance criterion: NMT 0.5%

Choline Chloride

(2-Hydroxyethyl)trimethylammonium Chloride



$C_5H_{14}ClNO$ Formula wt 139.65

INS: 1001(iii) CAS: [67-48-1]

DESCRIPTION

Choline Chloride occurs as colorless or white crystals or as a crystalline powder. It is hygroscopic, and is very soluble in water and in alcohol.

Function Nutrient

Packaging and Storage Store in tight containers.

IDENTIFICATION

• **A. CHLORIDE,** Appendix IIIA

Sample solution: 50 mg/mL

Acceptance criterion: Passes tests.

• **B. PROCEDURE**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 2 mL of water, add 3 mL of 1 N sodium hydroxide, and heat to boiling.

Acceptance criterion: The odor of trimethylamine is detectable.

• **C. PROCEDURE**

Sample: 500 mg

Analysis: Dissolve the *Sample* in 2 mL of iodine TS. A red-brown precipitate forms immediately. Add 5 mL of 1 N sodium hydroxide. The precipitate dissolves, and the solution becomes clear yellow. Heat the solution.

Acceptance criterion: A pale yellow precipitate forms following the heating step.

• **D. PROCEDURE**

Sample solution: 10 mg/mL

Analysis: Add 1 mL of the *Sample solution* and 2 mL of a 20 mg/mL solution of potassium ferrocyanide to 2 mL of cobaltous chloride TS.

Acceptance criterion: An emerald green color develops immediately.

ASSAY

• **PROCEDURE**

Sample: 300 mg

Analysis: Transfer the *Sample* into a 250-mL Erlenmeyer flask. Add 50 mL of glacial acetic acid and warm on a steam bath until dissolution is complete. Cool, add 10 mL of mercuric acetate and 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid in glacial acetic acid to a green endpoint. [**CAUTION:** Handle perchloric acid in an appropriate fume hood.] Perform a blank determination (see *General Provisions*), and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 13.96 mg of $C_5H_{14}ClNO$.

Acceptance criteria: NLT 98.0% and NMT 100.5% of $C_5H_{14}ClNO$, calculated on the anhydrous basis

IMPURITIES

Inorganic Impurities

- **LEAD,** *Lead Limit Test, Flame Atomic Absorption Spectrophotometric Method,* Appendix IIIB
  Sample: 5 g
  Acceptance criterion: NMT 2 mg/kg
- **WATER,** *Water Determination,* Appendix IIB
  [NOTE: Alternatively, the *Water Determination* can be made by drying the sample in a vacuum desiccator over phosphorus pentoxide for 4 h.]
  Acceptance criterion: NMT 0.5%

Organic Impurities

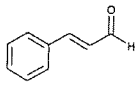
- **1,4-DIOXANE,** Appendix IIIB
  Acceptance criterion: Passes test.

SPECIFIC TESTS

- **RESIDUE ON IGNITION (SULFATED ASH),** Appendix IIC
  Sample: 4 g
  Acceptance criterion: NMT 0.05%

Cinnamaldehyde

Cinnamal
Cinnamic Aldehyde



C_9H_8O Formula wt 132.16
FEMA: 2286

DESCRIPTION

Cinnamaldehyde occurs as a yellow, strongly refractive liquid.
Odor Cinnamon, burning aromatic taste
Solubility Miscible in alcohol, chloroform, ether, fixed and volatile oils; 1 g dissolves in 700 mL water.
Boiling Point ~248°
Solubility in Alcohol, Appendix VI
One mL dissolves in 5 mL of 60% alcohol.
Function Flavoring agent

IDENTIFICATION

- **INFRARED SPECTRA,** *Spectrophotometric Identification Tests,* Appendix IIIC
  Acceptance criterion: The spectrum of the sample exhibits relative maxima at the same wavelengths as those of the spectrum below.

ASSAY

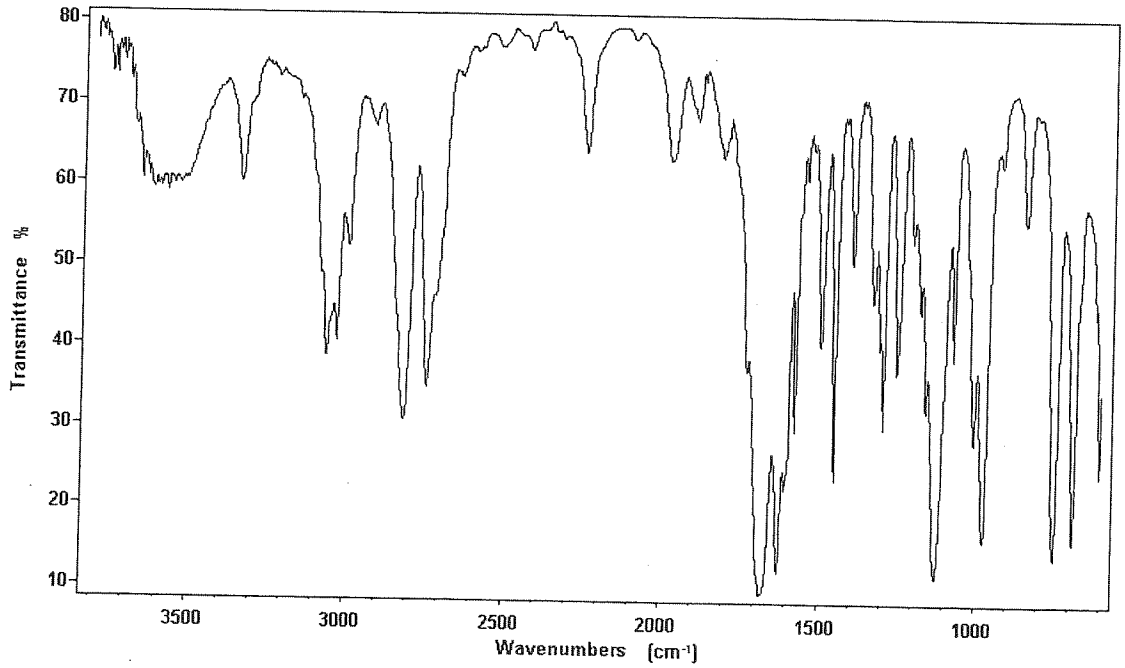
- **PROCEDURE** Proceed as directed under *M-1b,* Appendix XI.
  Acceptance criterion: NLT 98.0% of C_9H_8O

SPECIFIC TESTS

- **ACID VALUE,** *M-15,* Appendix XI
  Acceptance criterion: NMT 10.0
- **REFRACTIVE INDEX,** Appendix II (at 20°)
  Acceptance criterion: Between 1.619 and 1.623
- **SPECIFIC GRAVITY** Determine at 25° by any reliable method (see *General Provisions*).
  Acceptance criterion: Between 1.046 and 1.050

OTHER REQUIREMENTS

- **CHLORINATED COMPOUNDS,** Appendix VI
  Acceptance criterion: Passes test.



Cinnamaldehyde

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FOOD CHEMICALS CODEX

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By authority of the United States Pharmacopeial Convention. Prepared by the Council of Experts and published by the Board of Trustees

THE UNITED STATES PHARMACOPEIAL CONVENTION
12601 Twinbrook Parkway, Rockville, MD 20852

Evaluations of the Joint FAO/WHO Expert Committee on Food Additives (JECFA)

CHOLINE SALTS

General Information

INS: 1001

Functional Class:

- Food Additives
  - EMULSIFIER
  - FLAVOUR_ENHANCER
  - SALT_SUBSTITUTE

Evaluations

Evaluation year:	**1971**
ADI:	NOT LIMITED
Comments:	Use limited by good manufacturing practice
Meeting:	15
Specs Code:	O
Report:	NMRS 50/TRS 488-JECFA 15/16
Tox Monograph:	NOT PREPARED
Specification:	NOT PREPARED

Appendix F. Labels of products that contain the petitioned substance.


Your Child May Be Ready
If She or He:
• Sits independently
• Shows excitement when food is presented
Start Your Child on a Course to Healthy Nutrition
Nestlé
Start Healthy Stay Healthy
Good For Babies
• 38mg DHA & 25mg Choline per serving for Healthy Brain & Eye Development
• Excellent source of protective antioxidant Vitamin C to help support baby's natural defenses.
• As Healthy As Fresh Fruit
Nutritional Compass™
Made For Babies
Helps baby discover the taste of natural fruit to encourage healthy eating habits
SmartNourish™ is a smart choice for feeding your baby
2nd Foods
Gerber
organic
Bananas
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
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8-18-2008-


Your Child May Be Ready
If She or He:
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Start Your Child on a Course to Healthy Nutrition
Nestlé
Start Healthy Stay Healthy
Good For Babies
• 18mg DHA & 25mg Choline per serving for Healthy Brain & Eye Development
• Excellent source of protective antioxidant Vitamin A (from beta carotene) to help support baby's natural defenses
• As Healthy As Fresh Fruits & Vegetables
Made For Babies
Helps baby discover the taste of natural fruit & vegetables to encourage healthy eating habits
Nutritional Compass™
SmartNourish™ is a smart choice for feeding your baby
2nd Foods
Gerber
organic
Apple Sweet Potato
sitter
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
Certified Organic by Oregon Tilth
SEE INSIDE FOR MICROWAVE INSTRUCTIONS
REFRIGERATE AFTER OPENING
USE WITHIN 2-3 DAYS AFTER OPENING
Do not use if foil Seal is Broken or Missing.
Nutrition Facts
Amount Per Serving
Total Fat 1g
Trans Fat 0g
Total Carb 18g
Fiber 1g
Sodium 5mg
Sugars 11g
Potassium 115mg
Protein <1g
Calories 50
% Daily Value • Protein 0% • Vitamin A 45% (100% from beta carotene) • Vitamin C 45% • Calcium 0% • Iron 6% • Vitamin E 35% • Zinc 0%
INGREDIENTS: ORGANIC APPLES, ORGANIC SWEET POTATOES, WATER, TUNA OIL (SOURCE OF DHA), ASCORBIC ACID (VITAMIN C), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
Gerber Products Company • Fremont, MI 49413, USA
Ask our Experts 24/7: 1-800-4-GERBER • www.gerber.com
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Nestlé
Start Healthy Stay Healthy
Good For Babies
• 18mg DHA & 25mg Choline per serving for Healthy Brain & Eye Development
• As Healthy As Fresh Vegetables
• 2g Fiber per serving
Made For Babies
Helps baby discover the taste of natural vegetables to encourage healthy eating habits
Nutritional Compass™
SmartNourish™ is a smart choice for feeding your baby
2nd Foods
Gerber
organic
Green Beans
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
Certified Organic by Oregon Tilth
Gerber Products Company • Fremont, MI 49413, USA
Ask our Experts 24/7: 1-800-4-GERBER • www.gerber.com
Nutrition Facts
Serving Size 1 pack
Servings Per Container 2 packs
Amount Per Serving
Calories 35
Total Fat 0g
Trans Fat 0g
Total Carb 8g
Fiber 2g
Sodium 10mg
Sugars 3g
Potassium 180mg
Protein 2g
% Daily Value • Protein 4% • Vitamin A 15% • Vitamin C 6%
Calcium 0% • Iron 4% • Vitamin E 20% • Zinc 4%
INGREDIENTS: ORGANIC GREEN BEANS, WATER, TUNA OIL (SOURCE OF DHA), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
REFRIGERATE AFTER OPENING
USE WITHIN 2-3 DAYS AFTER OPENING
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Your Child May Be Ready

If She or He:

- Sits independently
- Shows excitement when food is presented

Start Your Child on a Course to Healthy Nutrition

Nestlé Start Healthy Stay Healthy

Good For Babies

- 18mg DHA & 25mg Choline per serving for Healthy Brain & Eye Development
- Excellent source of protective antioxidant Vitamin A (from beta carotene) to help support baby's natural defenses
- As Healthy As Fresh Vegetables

Made For Babies

Helps baby discover the taste of natural vegetables to encourage healthy eating habits

Nutritional Compass™

SmartNourish™ is a smart choice for feeding your baby

2nd Foods

Gerber

organic Butternut Squash & Corn

2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)

SmartNourish

DHA & Choline helps support **BRAIN & EYE DEVELOPMENT**

USDA ORGANIC

PATENT PENDING

Certified Organic by Oregon Tilth

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USE WITHIN 2-3 DAYS AFTER OPENING
Do not use if foil seal is broken or Missing.

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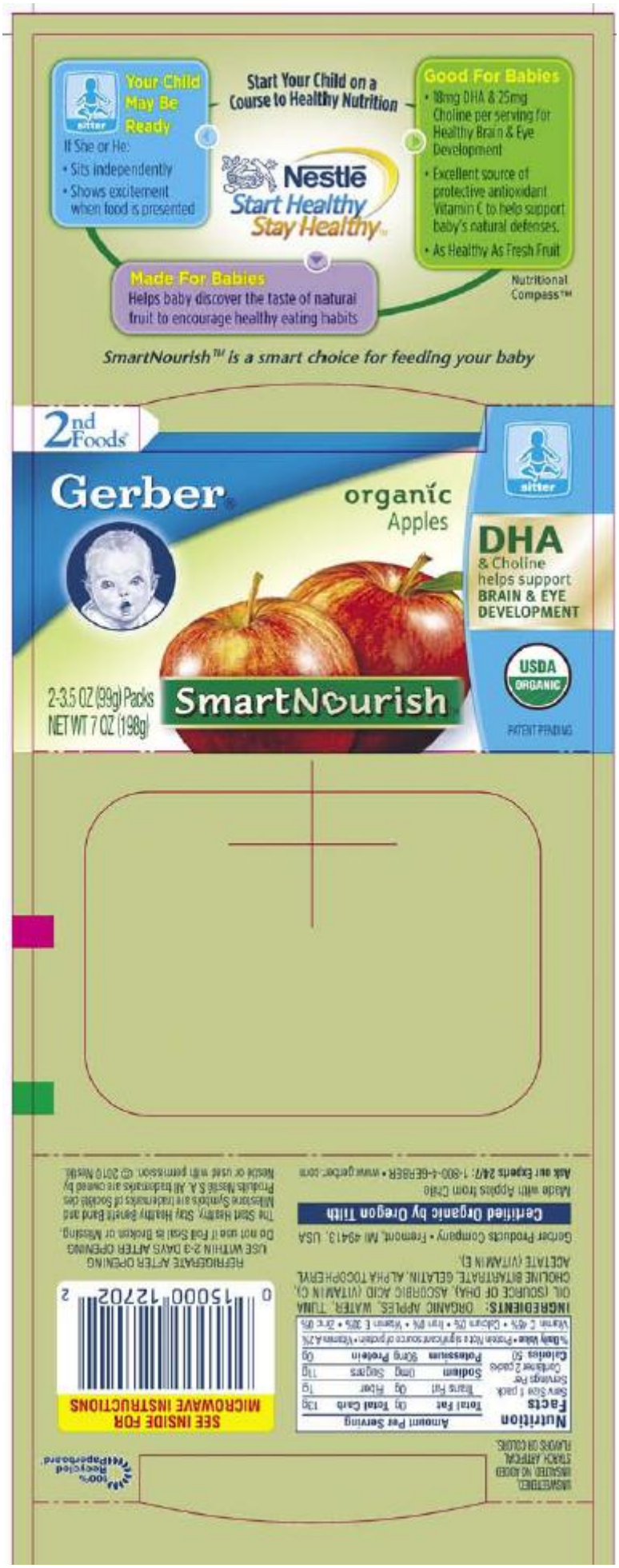
100% Recycled Paperboard

INGREDIENTS: ORGANIC BUTTERNUT SQUASH, WATER, ORGANIC CORN, TUNA OIL (SOURCE OF DHA), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).

MANUFACTURED, INSPECTED, NO ADDED STARCH, ARTIFICIAL FLAVORS OR COLORS.

4328507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& Choline helps support BRAIN & EYE DEVELOPMENT
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SmartNourish
Certified Organic by Oregon Tilth
Made with Apples from Chile
Ask an Expert 24/7: 1-800-4-GERBER • www.gerber.com
Gerber Products Company • Fremont, MI 49413, USA
INGREDIENTS: ORGANIC APPLES, WATER, TUNA OIL (SOURCE OF DHA), ASCORBIC ACID (VITAMIN C), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
Nutrition Facts
Amount Per Serving
Total Fat 1.5g
Total Carb 13g
Sodium 0mg
Potassium 50mg
Protein 0g
Calories 50
Vitamin C 40% • Calcium 0% • Iron 8% • Vitamin E 30% • Zinc 0%
*Daily Value • Tuna is a significant source of protein • Vitamin A 2%
REFRIGERATE AFTER OPENING
USE WITHIN 2-3 DAYS AFTER OPENING
Do not use if foil Seal is Broken or Missing.
SEE INSIDE FOR MICROWAVE INSTRUCTIONS
100% Recycled Paperboard
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USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
SEE INSIDE FOR MICROWAVE INSTRUCTIONS
0 15000 12705 3
Nutrition Facts
Amount Per Serving
INGREDIENTS: ORGANIC APPLES, ORGANIC STRAWBERRY PUREE, WATER, TUMA OIL, ISOLUBCE OF DHA), ASCORBIC ACID (VITAMIN C), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
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• Shows excitement when food is presented
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Nestlé
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Stay Healthy
Good For Babies
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Helps baby discover the taste of natural fruit to encourage healthy eating habits
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2nd Foods
Gerber
organic
Pears
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA
ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
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Made with Pears from Argentina
Ask our Experts 24/7: 1-800-4-GERBER • www.gerber.com
Gerber Products Company • Fremont, MI 49413, USA
INGREDIENTS: ORGANIC PEARS, WATER, TUVA OIL (SOURCE OF DHA), ASCORBIC ACID (VITAMIN C), CHOLINE BITARTRATE, GELATIN, CITRIC ACID, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
Nutrition Facts
Serv Size 1 pack
Container 2 packs
Calories 80
Total Fat 0g
Trans Fat 0g
Saturated Fat 0g
Sodium 5mg
Total Carb 15g
Fiber 2g
Sugars 10g
Potassium 110mg
Protein <1g
% Daily Value • Protein Not a significant source of protein • Vitamin A 0%
Vitamin C 40% • Calcium 0% • Iron 0% • Vitamin E 20% • Zinc 0%
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Your Child May Be Ready
If She or He:
• Sits independently
• Shows excitement when food is presented
Start Your Child on a Course to Healthy Nutrition
Nestlé
Start Healthy
Stay Healthy
Good For Babies
• 18mg DHA & 25mg Choline per serving For Healthy Brain & Eye Development
• Excellent source of protective antioxidant Vitamin C to help support baby's natural defenses.
• As Healthy As Fresh Fruit
Nutritional Compass™
Made For Babies
Helps baby discover the taste of natural fruit to encourage healthy eating habits
SmartNourish™ is a smart choice for feeding your baby
2nd Foods
Gerber
organic
Pears
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA
ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
Certified Organic by Oregon Tilth
SEE INSIDE FOR
MICROWAVE INSTRUCTIONS
0 15000 12704 6


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organic
Pear & Wild Blueberry
DHA
& Choline helps support BRAIN & EYE DEVELOPMENT
USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
Nutrition Facts
Amount Per Serving
Total Fat 1.5g
Trans Fat 0g
Total Carb 15g
Fiber 2g
Sodium 10mg
Sugars 16g
Potassium 110mg
Protein <1g
INGREDIENTS: ORGANIC PEARS, ORGANIC WILD BLUEBERRIES, WATER, TUNA OIL (SOURCE OF DHA), ASCORBIC ACID (VITAMIN C), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
Certified Organic by Oregon Tilth
Gerber Products Company • Fremont, MI 49413, USA
Ask our Experts 24/7: 1-800-4-GERBER • www.gerber.com
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NET WT 7 OZ (198g)
SmartNourish
Nutrition Facts
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Total Carb
Sodium
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INGREDIENTS:
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Made For Babies
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Nutritional Compass™
SmartNourish™ is a smart choice for feeding your baby
2nd Foods
Gerber
organic
Carrots
DHA
& Choline
helps support
BRAIN & EYE
DEVELOPMENT
USDA ORGANIC
PATENT PENDING
2-3.5 OZ (99g) Packs
NET WT 7 OZ (198g)
SmartNourish
Nutrition Facts
Amount Per Serving
Total Fat 5g
Total Carb 6g
Sodium 75mg
Potassium 230mg
Protein <1g
Calories 40
% Daily Value
INGREDIENTS: ORGANIC CARROTS, WATER, TUNA OIL (SOURCE OF DHA), CHOLINE BITARTRATE, GELATIN, ALPHA TOCOPHERYL ACETATE (VITAMIN E).
Certified Organic by Oregon Tilth
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Gerber
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Sweet Potatoes
DHA
& Choline
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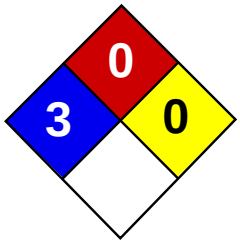
Appendix G. Material Safety Data Sheet for choline hydroxide.

Material Safety Data Sheet for choline bitartrate.

Material Safety Data Sheet for choline chloride.



Material Safety Data Sheet
Choline Hydroxide MSDS

Section 1: Chemical Product and Company Identification

Product Name: Choline Hydroxide

Catalog Codes: SLC4774

CAS#: Mixture.

RTECS: GA4025500

TSCA: TSCA 8(b) inventory: Choline Hydroxide; Water

CI#: Not available.

Synonym: Bursine, Fagine, Gossypine, Luridine, Sincaline, Vidine; Ethanaminium, 2-hydroxy-N,N,N-trimethyl-, hydroxide; 2-Hydroxyethyltrimeethylammonium Hydroxide

Chemical Name: Choline Hydroxide

Chemical Formula: C5-H15-N-O2

Contact Information:

Sciencelab.com, Inc.
14025 Smith Rd.
Houston, Texas 77396

US Sales: **1-800-901-7247**
International Sales: **1-281-441-4400**

Order Online: ScienceLab.com

CHEMTREC (24HR Emergency Telephone), call: 1-800-424-9300

International CHEMTREC, call: 1-703-527-3887

For non-emergency assistance, call: 1-281-441-4400

Section 2: Composition and Information on Ingredients

Composition:

Name	CAS #	% by Weight
Water	7732-18-5	50-55
Choline Hydroxide	123-41-1	45-50

Toxicological Data on Ingredients: Choline Hydroxide LD50: Not available. LC50: Not available.

Section 3: Hazards Identification

Potential Acute Health Effects:
Very hazardous in case of skin contact (irritant), of eye contact (irritant), of ingestion, . Hazardous in case of skin contact (corrosive), of eye contact (corrosive). Non-corrosive for lungs. Liquid or spray mist may produce tissue damage particularly on mucous membranes of eyes, mouth and respiratory tract. Skin contact may produce burns. Inhalation of the spray mist may produce severe irritation of respiratory tract, characterized by coughing, choking, or shortness of breath. Inflammation of the eye is characterized by redness, watering, and itching. Skin inflammation is characterized by itching, scaling, reddening, or, occasionally, blistering.

Potential Chronic Health Effects:
Non-corrosive for skin. Non-irritant for skin. Non-sensitizer for skin. Non-permeator by skin. Non-irritating to the eyes. Non-hazardous in case of ingestion. Non-hazardous in case of inhalation. Non-irritant for lungs. Non-sensitizer for lungs.

CARCINOGENIC EFFECTS: Not available. MUTAGENIC EFFECTS: Not available. TERATOGENIC EFFECTS: Not available. DEVELOPMENTAL TOXICITY: Not available. Repeated or prolonged contact with spray mist may produce chronic eye irritation and severe skin irritation. Repeated or prolonged exposure to spray mist may produce respiratory tract irritation leading to frequent attacks of bronchial infection.

Section 4: First Aid Measures

Eye Contact:
Check for and remove any contact lenses. In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Cold water may be used. Get medical attention immediately.

Skin Contact:
In case of contact, immediately flush skin with plenty of water for at least 15 minutes while removing contaminated clothing and shoes. Cover the irritated skin with an emollient. Cold water may be used.Wash clothing before reuse. Thoroughly clean shoes before reuse. Get medical attention immediately.

Serious Skin Contact:
Wash with a disinfectant soap and cover the contaminated skin with an anti-bacterial cream. Seek medical attention.

Inhalation:
If inhaled, remove to fresh air. If not breathing, give artificial respiration. If breathing is difficult, give oxygen. Get medical attention immediately.

Serious Inhalation:
Evacuate the victim to a safe area as soon as possible. Loosen tight clothing such as a collar, tie, belt or waistband. Seek medical attention.

Ingestion:
Do NOT induce vomiting unless directed to do so by medical personnel. Never give anything by mouth to an unconscious person. If large quantities of this material are swallowed, call a physician immediately. Loosen tight clothing such as a collar, tie, belt or waistband.

Serious Ingestion: Not available.

Section 5: Fire and Explosion Data

Flammability of the Product: May be combustible at high temperature.

Auto-Ignition Temperature: Not available.

Flash Points: Not available.

Flammable Limits: Not available.

Products of Combustion: Not available.

Fire Hazards in Presence of Various Substances:
Slightly flammable to flammable in presence of heat. Non-flammable in presence of open flames and sparks, of shocks, of oxidizing materials, of reducing materials, of combustible materials, of organic materials, of metals, of acids, of alkalis.

Explosion Hazards in Presence of Various Substances: Non-explosive in presence of open flames and sparks, of shocks.

Fire Fighting Media and Instructions:
SMALL FIRE: Use DRY chemical powder. LARGE FIRE: Use water spray, fog or foam. Do not use water jet.

Special Remarks on Fire Hazards: Not available.

Special Remarks on Explosion Hazards: Not available.

Section 6: Accidental Release Measures

Small Spill:
Dilute with water and mop up, or absorb with an inert dry material and place in an appropriate waste disposal container.

Large Spill:
Corrosive liquid. Stop leak if without risk. Absorb with DRY earth, sand or other non-combustible material. Do not get water inside container. Do not touch spilled material. Use water spray curtain to divert vapor drift. Prevent entry into sewers, basements or confined areas; dike if needed. Eliminate all ignition sources. Call for assistance on disposal.

Section 7: Handling and Storage

Precautions:
Keep container dry. Keep away from heat. Keep away from sources of ignition. Empty containers pose a fire risk, evaporate the residue under a fume hood. Ground all equipment containing material. Do not breathe gas/fumes/ vapor/spray. Never add water to this product. In case of insufficient ventilation, wear suitable respiratory equipment. If you feel unwell, seek medical attention and show the label when possible. Avoid contact with skin and eyes. Keep away from incompatibles such as oxidizing agents.

Storage: Keep container tightly closed. Keep container in a cool, well-ventilated area.

Section 8: Exposure Controls/Personal Protection

Engineering Controls:
Provide exhaust ventilation or other engineering controls to keep the airborne concentrations of vapors below their respective threshold limit value. Ensure that eyewash stations and safety showers are proximal to the work-station location.

Personal Protection:
Face shield. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Gloves. Boots.

Personal Protection in Case of a Large Spill:
Splash goggles. Full suit. Vapor respirator. Boots. Gloves. A self contained breathing apparatus should be used to avoid inhalation of the product. Suggested protective clothing might not be sufficient; consult a specialist BEFORE handling this product.

Exposure Limits: Not available.

Section 9: Physical and Chemical Properties

Physical state and appearance: Liquid.

Odor: Not available.

Taste: Not available.

Molecular Weight: 121.18

Color: Amber.

pH (1% soln/water): Neutral.

Boiling Point: The lowest known value is 100°C (212°F) (Water).

Melting Point: Not available.

Critical Temperature: Not available.

Specific Gravity: 1.073 (Water = 1)

Vapor Pressure: The highest known value is 2.3 kPa (@ 20°C) (Water).

Vapor Density: The highest known value is 0.62 (Air = 1) (Water).

Volatility: Not available.

Odor Threshold: Not available.

Water/Oil Dist. Coeff.: Not available.

Ionicity (in Water): Not available.

Dispersion Properties: See solubility in water.

Solubility: Easily soluble in cold water, hot water.

Section 10: Stability and Reactivity Data

Stability: The product is stable.

Instability Temperature: Not available.

Conditions of Instability: Excess heat, incompatible materials

Incompatibility with various substances: Reactive with oxidizing agents.

Corrosivity: Non-corrosive in presence of glass.

Special Remarks on Reactivity: Absorbs CO2 from air.

Special Remarks on Corrosivity: Not available.

Polymerization: Will not occur.

Section 11: Toxicological Information

Routes of Entry: Absorbed through skin. Eye contact. Inhalation. Ingestion.

Toxicity to Animals:
LD50: Not available. LC50: Not available.

Chronic Effects on Humans: Not available.

Other Toxic Effects on Humans:
Very hazardous in case of skin contact (irritant), of ingestion, . Hazardous in case of skin contact (corrosive), of eye contact (corrosive), of inhalation (lung corrosive).

Special Remarks on Toxicity to Animals: Not available.

Special Remarks on Chronic Effects on Humans: Not available.

Special Remarks on other Toxic Effects on Humans:
Acute Potential Health Effects: Skin: Causes skin burns Eyes: Causes eye burns. May cause corneal damage or blindness Inhalation: May cause severe respiratory tract and mucous membrane irritation. Inhalation may result in spasm, inflammation and edema of the bronchi, and larynx, chemical pneumonitis, and pulmonary edema. Symptoms may include burning sensation, coughing, wheezing, laryngitis, shortness of breath, headache, nausea and vomiting. Ingestion: Harmful if swallowed. May cause severe digestive tract irritation with abdominal pain, nausea, and vomiting, and possible burns of the mouth and throat. May affect behavior (convulsions, excitement), and respiration (dyspnea). The toxicological properties of this substance have not been fully investigated.

Section 12: Ecological Information

Ecotoxicity: Not available.

BOD5 and COD: Not available.

Products of Biodegradation:

Possibly hazardous short term degradation products are not likely. However, long term degradation products may arise.

Toxicity of the Products of Biodegradation: Not available.

Special Remarks on the Products of Biodegradation: Not available.

Section 13: Disposal Considerations

Waste Disposal:
Evaporate water from the solution at water-aspirator pressure. Maintain heating bath temperature <50 C. Dissolve the residue in a combustible solvent and burn in a chemical incinerator equipped with an afterburner and scrubber. Waste must be disposed of in accordance with federal, state and local environmental control regulations.

Section 14: Transport Information

DOT Classification: Class 8: Corrosive material

Identification: : Amine, liquid, corrosive, n.o.s. (Choline Hydroxide) (Choline Hydroxide) UNNA: 2735 PG: II

Special Provisions for Transport: Not available.

Section 15: Other Regulatory Information

Federal and State Regulations: TSCA 8(b) inventory: Choline Hydroxide; Water

Other Regulations:
OSHA: Hazardous by definition of Hazard Communication Standard (29 CFR 1910.1200). EINECS: This product is on the European Inventory of Existing Commercial Chemical Substances.

Other Classifications:

WHMIS (Canada): Not controlled under WHMIS (Canada).

DSCL (EEC):
R34- Causes burns. S26- In case of contact with eyes, rinse immediately with plenty of water and seek medical advice. S27- Take off immediately all contaminated clothing. S28- After contact with skin, wash immediately with plenty of water. S36/37/39- Wear suitable protective clothing, gloves and eye/face protection. S45- In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).

HMIS (U.S.A.):

Health Hazard: 3

Fire Hazard: 1

Reactivity: 0

Personal Protection:

National Fire Protection Association (U.S.A.):

Health: 3

Flammability: 0

Reactivity: 0

Specific hazard:

Protective Equipment:
Gloves. Full suit. Vapor respirator. Be sure to use an approved/certified respirator or equivalent. Face shield.

Section 16: Other Information

References: Not available.

Other Special Considerations: Not available.

Created: 10/09/2005 04:54 PM

Last Updated: 11/06/2008 12:00 PM

American International Chemical, Inc.

Corporate Offices: (800) 238-0001
Internet: www.aicma.com *Email:* info@aicma.com

MATERIAL SAFETY DATA SHEET

CHOLINE BITARTRATE

SECTION 1 - CHEMICAL PRODUCT AND COMPANY INFORMATION

American International Chemical, Inc.	**Emergency Number: Chemtrec**	**800-424-9300**
135 Newbury Street		**703-527-3887**
Framingham, MA 01701	**Information Number:**	**800-238-0001**

Date: August 2007

Synonyms: None

CAS #: 87-67-2 and 132215-92-0

DOT Hazard Class: Not Regulated

SECTION 2 - COMPOSITION AND INFORMATION ON INGREDIENTS

Choline Bitartrate	99% min.
Silica	1% max.

SECTION 3 - HAZARDS IDENTIFICATION

EMERGENCY OVERVIEW: White crystalline free flowing powder. It presents little or no health hazard and no unusual hazard if involved in a fire.

POTENTIAL HEALTH EFFECTS:
Skin: May cause skin irritation.
Eyes: May cause irritation or burning.
Inhalation: May cause irritation to the respiratory tract.
Ingestion: Not a hazard with normal industrial usage.

SECTION 4 - FIRST AID MEASURES

Skin: Immediately wash skin with soap and water for at least 15 minutes.
Eyes: Immediately flush with plenty of water for at least 15 minutes, holding eye lids apart.
Inhalation: Remove to the fresh air. If not breathing give artificial respiration. If breathing is difficult, give oxygen.
Ingestion: Wash out mouth with water.
On All Of The Above: Consult a physician if symptoms persist.

SECTION 5 - FIRE FIGHTING MEASURES

Flash Point: Non Combustible

Flammable Limits: Not Applicable

Extinguishing Media: Use media that is appropriate to treat surrounding fire.

Special Fire Fighting Procedures:
Use fire fighting procedure that is appropriate to treat surrounding fire. All firefighters should use self-contained breathing apparatus and full fire-fighting turn-out gear.

Unusual Fire Explosion Hazard: None known

Auto Ignition Temperature: Not Applicable

SECTION 6 - ACCIDENTAL RELEASE MEASURES

Isolate hazard area and deny entry to unnecessary or unprotected personnel. Contain spill, sweep up, collect and place in a disposal container. Avoid runoff into storm sewers and ditches which lead to waterways.

SECTION 7 - HANDLING AND STORAGE

Avoid contact with skin, eyes and clothing. Use with adequate ventilation. Avoid breathing dust . Use normal personal hygiene and housekeeping. Store in cool dry area away from other incompatible materials. Product is slightly hygroscopic and should be stored in a dry area to prevent moisture pick up and caking.

SECTION 8 - EXPOSURE CONTROLS, PERSONAL PROTECTION

RESPIRATORY PROTECTION: Use NIOSH/MSHA approved respirators.

VENTILATION REQUIREMENTS: Ventilate as necessary to eliminate dust from the work area and maintain concentrations below the limit.

SKIN AND EYE PROTECTION: Use rubber or neoprene gloves, chemical goggles and clothing sufficient to protect skin from dust.

WORK, HYGIENIC PRACTICES:
As required to protect skin and eyes from dust, safety showers and/or eye wash should be available. Do not leave food or smoke in work area. Wash thoroughly and remove or clean any contaminated clothing.

EXPOSURE LIMITS: None Established

SECTION 9 - PHYSICAL AND CHEMICAL PROPERTIES

Boiling Point: Not Applicable

Vapor Pressure (MM Hg): Not Applicable

Vapor Density (AIR=1): Not Applicable

Specific Gravity (H_20=1): Not Available

Percent Volatile by Volume (%): Not Applicable

Melting Point: 150 °C

Evaporation Rate (Butyl Acetate=1): Not Applicable

Solubility in Water: Complete (except for Silica, which is insoluble in water)

pH: Not Available

SECTION 10 - STABILITY AND REACTIVITY

CHEMICAL STABILITY: Stable under normal temperatures and pressures.

HAZARDOUS POLYMERIZATION: Will not occur under normal conditions.

HAZARDOUS DECOMPOSITION PRODUCTS: Combustion may produce Carbon Dioxide and Carbon Monoxide.

KEEP AWAY FROM: None known.

SECTION 11 - TOXICOLOGICAL INFORMATION

Not Available

SECTION 12 - ECOLOGICAL INFORMATION

Not Available

SECTION 13 - DISPOSAL CONSIDERATIONS

Dispose of in accordance with all federal, state and local regulations.

RCRA WASTE #: Not Listed

SECTION 14 - TRANSPORTATION INFORMATION

D.O.T. SHIPPING NAME: Choline Bitartrate

SECTION 15 - REGULATORY INFORMATION

OSHA STATUS: Not listed

TSCA STATUS: Listed

CERCLA REPORTABLE REQUIREMENTS: (RQ) None

SARA TITLE III INFORMATION:

Section 302 Extremely Hazardous Substance Not listed

Section 313 Toxic Chemicals: Not listed

Section 311/312 Hazard Category: Not considered a Hazard.

SECTION 16 - OTHER INFORMATION

Not Available

Reason for Issue: Changed Date

This information is given without any warranty or representation. It is believed to be correct but does not claim to be all inclusive and shall be used only as a guide. American International Chemical, Inc., shall not be held liable for any damage resulting from handling or contact with the above product. It is offered solely for your consideration, investigation and verification.

CHOLINE CHLORIDE

ICSC: 0853

Date of Peer Review: October 2005

(2-Hydroxyethyl)trimethylammonium chloride
Choline hydrochloride
2-Hydroxy-N,N,N-trimethylethanaminium chloride
Cholinium chloride

CAS #	67-48-1	$C_5H_{14}NO.Cl$
RTECS #	KH2975000	Molecular mass: 139.6
UN #		
EC Index #		

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Water spray, powder.
EXPLOSION			
EXPOSURE			
Inhalation		Ventilation.	Fresh air, rest.
Skin		Protective gloves.	Rinse and then wash skin with water and soap.
Eyes		Safety spectacles.	Rinse with plenty of water for several minutes (remove contact lenses if easily possible).
Ingestion		Do not eat, drink, or smoke during work.	

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting.	**EU Classification** **UN Classification**
EMERGENCY RESPONSE	**STORAGE**
	Separated from strong oxidants.

IPCS
International Programme on Chemical Safety

UNEP

SEE IMPORTANT INFORMATION ON BACK

CHOLINE CHLORIDE	**ICSC: 0853**

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE: WHITE HYGROSCOPIC CRYSTALS **CHEMICAL DANGERS:** On combustion, forms toxic and corrosive fumes including hydrogen chloride. Reacts with strong oxidants. **OCCUPATIONAL EXPOSURE LIMITS:** TLV not established. MAK not established.	**INHALATION RISK:** A nuisance-causing concentration of airborne particles can be reached quickly when dispersed.

PHYSICAL PROPERTIES

Melting point: 305°C Solubility in water: miscible	Octanol/water partition coefficient as log Pow: -5.16

ENVIRONMENTAL DATA

NOTES

ADDITIONAL INFORMATION

See Also:
Toxicological Abbreviations
Choline chloride (SIDS)