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(54) Title: COMPOSITIONS AND METHODS OF FORMULATION FOR ENTERAL FORMULAS CONTAINING SIALIC ACID

(57) Abrégé/Abstract:
A nutritionally complete infant formula containing sialic acid derived from one or a number of nutritionally appropriate sources is described. The infant formula comprises CGMP having an enhanced concentration of sialic acid.

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(54) Title: COMPOSITIONS AND METHODS OF FORMULATION FOR ENTERAL FORMULAS CONTAINING SIALIC ACID

(57) Abstract: A nutritionally complete infant formula containing sialic acid derived from one or a number of nutritionally appropriate sources is described. The infant formula comprises CGMP having an enhanced concentration of sialic acid.

# COMPOSITIONS AND METHODS OF FORMULATION FOR ENTERAL FORMULAS CONTAINING SIALIC ACID

## CROSS-REFERENCE TO RELATED PATENTS AND PATENT APPLICATION

**[0001]** This application is a continuation-in-part and claims the priority benefit of co-pending U.S. Patent Application Serial No. 10/413,508, filed April 14, 2003, which is incorporated herein to the extent that it does not conflict with the disclosures of the present application.

## BACKGROUND OF THE INVENTION

(1) Field of the Invention:

**[0002]** The present invention relates generally to infant's and children's nutritional formulas containing sialic acid and methods for manufacturing such formulas.

(2) Description of the Related Art:

**[0003]** Sialic acid (N-acetylneuraminic acid or NANA) is a naturally occurring component of human breast milk, where it is found associated with various oligosaccharides and glycoproteins. While human breast milk contains substantial amounts of sialic acid, most infant formulas contain less than 25% of the sialic acid found in colostrum. Moreover, 70% of the sialic acid in formulas is glycoprotein-bound, unlike human breast milk in which 75% of sialic acid is bound to oligosaccharides. See Heine, W., *et al., Monatsschr Kinderheilkd* 141:946-50 (1993), Wang, B., *et al., Am J Clin Nutr* 74:510-5 (2001), and Nakano, T., *et al., Acta Paediatr Taiwan* 42:11-17 (2001). Not surprisingly, the accumulation of sialic acid by breast-fed infants is generally higher than for formula-fed infants. See Wang, B., *et al., J Pediatr* 138:914-6 (2001). Evidence suggests that sialic acid is important in the development and function of the neonatal brain where it is a major component of gangliosides. See Carlson, S.E., *Am J Clin Nutr* 41:720-6 (1985), Morgan, B. and Winnick, M., *J Nutr* 110:416-24 (1980), Svennerholm, L., *et al., Biochim Biophys Acta* 1005:109-17 (1989),

and Wang, B., *et al., Comp Biochem Physiol A Mol Integr Physiol* 435-9 (1998).

**[0004]** Cow's milk-based formulas generally have low sialic acid content. In one study, the concentration of sialic acid in several casein/whey combination formulas was less than 200 mg sialic acid/L. Moreover, soy protein-based formulas contain substantially reduced levels of sialic acid as compared to cow's milk-based formula. Therefore, formulas that are both lactose free and soy protein-based would exhibit very low sialic acid content.

**[0005]** There are several known sources of sialic acid in its various conjugated forms. These include, but are not limited to, free N-acetylneuraminic acid (or sialic acid), the oligosaccharide sialyllactose, sialic acid-containing gangliosides, and the protein casein macropeptide (CMP), also referred to as glycomacropeptide (GMP), and caseinoglycomacropeptide (cGMP).

**[0006]** The addition of sialic acid or sources of sialic acid to certain nutritional formulas has been mentioned in the art. For example, U.S. Patent No. 6,506,422 discloses a particular nutritional formula containing casein glycomacropeptide and complimentary essential amino acids other than phenylalanine for administration to patients suffering from phenylketonuria. The levels of sialic acid found in infant formulas are not mentioned.

**[0007]** U.S. Patent No. 6,270,827, discloses a formulation containing human milk proteins or recombinant host resistance factors, one of which is recombinant human kappa-casein, to supplement synthetic infant formulas.

**[0008]** U.S. Patent No. 4,762,822 discloses the use of N-acetylneuraminic acid or gangliosides containing sialic acid in infant formula to protect the newborn from gastrointestinal disease-producing organisms.

**[0009]** International patent application WO 01/60346 A2 discloses a nutritional formulation containing the oligosaccharides oligofructose and

sialyllactose as prebiotic substances to promote the growth of bifidobacteria in the gut that may be used in conjunction with infant formula.

**[00010]** While the use of sialic acid and sialic acid sources in infant formula is mentioned in the prior art, it would be useful to provide an infant formula having enhanced amounts of sialic acid similar to breast milk, and in particular, to provide infant formula that is nutritionally complete. Furthermore, it would be useful to provide infant formula having enhanced amounts of sialic acid while also providing an amino acid profile that is similar to breast milk.

## SUMMARY OF THE INVENTION

**[00011]** Briefly, the present invention is directed to a novel infant formula comprising a cGMP having an enhanced concentration of sialic acid.

**[00012]** The present invention is also directed to a novel infant formula comprising a cGMP having an enhanced concentration of sialic acid and a reduced level of threonine.

**[00013]** The present invention is also directed to a novel method of producing an infant formula comprising intermixing a cGMP having an enhanced concentration of sialic acid with sources of protein, carbohydrate and lipid sufficient to provide a nutritionally complete formula.

**[00014]** Accordingly, it has been found that the present invention provides an infant formula having enhanced amounts of sialic acid similar to breast milk, and in particular, an infant formula that is nutritionally complete, and also provides an infant formula having enhanced amounts of sialic acid while also providing an amino acid profile that is similar to breast milk, and in particular, an infant formula having a reduced threonine content.

## DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

**[00015]** Reference now will be made in detail to the embodiments of the invention, one or more examples of which are set forth below. Each example is provided by way of explanation of the invention, not limitation of the invention. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made in the present invention

without departing from the scope or spirit of the invention. For instance, features illustrated or described as part of one embodiment can be used on another embodiment to yield a still further embodiment.

**[00016]** Thus, it is intended that the present invention cover such modifications and variations as come within the scope of the appended claims and their equivalents. Other objects, features and aspects of the present invention are disclosed in or are obvious from the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only, and is not intended as limiting the broader aspects of the present invention.

**[00017]** It has been found that certain cGMP-based products having enhanced levels of sialic acid can be used to produce infant formula having an enhanced content of sialic acid. These formulas are suitable to support normal growth and development of infants and children. Specifically, the novel formulas include one or a combination of nutritionally appropriate source(s) of sialic acid having enhanced levels of sialic acid. The level of sialic acid in the formula is designed to mimic the total sialic acid found in breast milk over the period of 0 – 12 months of lactation.

**[00018]** Certain of the innovative aspects of the invention involve the use of novel cGMP-based products that contain levels of sialic acid that are higher than normally found in cGMP products that are now commercially available. These novel products can be used alone or in combination to achieve sialic acid levels that mimic that found in breast milk, based on the sialic acid content of the various source ingredients.

**[00019]** This invention is directed to a composition and a method of formulating milk protein-based formulas, both with and without lactose, non-milk-based formulas, including soy protein-based formulas, amino acid formulas, and rice protein formulas, that contain sialic acid at concentrations comparable to that found in human milk. The nature and novelty of the invention involves the appropriate selection of sialic acid-

containing ingredients to achieve both appropriate sialic acid levels as well as appropriate nutrients for specific infant and children's formulas.

**[00020]** For example, in cow's milk protein-based formulas that contain lactose, the supplemental sialic acid in this composition may come from one or a combination of sources, particularly free sialic acid (neuraminic acid), 3'-sialyllactose, 6'-sialyllactose, or other sialic acid-containing oligosaccharide, and casein glycomacropeptide (cGMP) or other sialic acid-containing milk protein fraction, including whey protein. The sialyllactose conjugate(s) used in this invention may replace a portion of the lactose customarily used in these formulations, while the casein glycomacropeptide (cGMP) and other milk protein fractions may replace a portion of the protein fraction of the formula. In the case of lactose-free formulas, which are also milk protein-free, free sialic acid, other non-cow's milk protein fractions containing sialic acid, or sialic acid-containing oligosaccharides other than lactose may be used. The fat, vitamin, and mineral concentrations of these compositions are otherwise nutritionally appropriate for infants. The total concentration of sialic acid in these formulations would mimic that found in breast milk and may typically be within a range of about 250 mg/L (as found in mature human breast milk) to about 1500 mg/L (as found in human colostrums).

**[00021]** The present invention provides a nutritionally complete formulation that includes one or more sources of sialic acid, in amounts which mimic the concentration of sialic acid found in human breast milk. The present invention additionally provides a method of making such formulations, in the form of milk protein-based formulas, both with and without lactose, non-milk-based formulas, including soy protein-based formulas, amino acid formulas, and rice protein formulas.

**[00022]** The form of administration of and incorporation of sialic acid in the method of the present invention is not critical, as long as an effective amount is administered. A convenient form of administration is to add sialic acid to an infant formula (including those for both term and preterm infants), follow-on formula, toddler's beverage, milk, yogurt, or fermented

product. Alternatively, sialic acid can be administered as a supplement that is not part of a formula feeding such as, for example, drops, sachets or combinations with other nutrients such as vitamins. Sialic acid can be also added to other nutrients suitable for feeding to young children such as, for example, solid baby food, fruit juices, gelatines, cookies, candies, etc. Other examples of administering sialic acid in nutrients can be developed by a person with ordinary skill in the art of infant and child nutrition. All these forms of sialic acid administration, as well as others, are within the scope of the present invention.

**[00023]** In one embodiment of the invention, sialic acid is administered as part of an infant formula. The infant formula for use in the present invention is, typically, nutritionally complete and contains suitable types and amounts of lipids, carbohydrates, proteins, vitamins and minerals. The amount of lipids or fats typically can vary from about 3 to about 7 g/100 kcal. The amount of proteins typically can vary from about 1 to about 5g/100 kcal. The amount of carbohydrates typically can vary from about 6 to about 16 g/100 kcal. Protein sources can be any used in the art, and may include, for example, nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, and amino acids. Lipid sources can be any used in the art such as, for example, vegetable oils such as palm oil, soybean oil, palm olein oil, corn oil, canola oil, coconut oil, medium chain triglyceride oils, high oleic sunflower oil, and high oleic safflower oil. Carbohydrate sources can be any known in the art such as, for example, lactose, glucose polymers, corn syrup solids, maltodextrins, sucrose, starch, and rice syrup solids.

**[00024]** The present invention is also directed to a novel method of producing an infant formula comprising intermixing a cGMP having an enhanced concentration of sialic acid with sources of protein, carbohydrate and lipid sufficient to provide a nutritionally complete formula. The high-sialic acid cGMP can be any of such products that are discussed herein, and the sources or protein, carbohydrate and lipid, along with any other

useful and desirable components that are normally found in infant formulas, are well known in the art.

**[00025]** Conveniently, several commercially available infant formulas can be used as the basic formula for the sialic acid or sialic acid-sources additions. For example, Enfamil® Lipil with iron (available from Mead Johnson & Company, Evansville, Indiana, U.S.A.) may be supplemented with an effective amount of sialic acid and used to practice the method of the present invention. Particular infant formulas suitable for use in the present invention are described in the Examples herein.

**[00026]** The total protein in the formulation from all protein sources should be nutritionally appropriate for infants, which is typically from about 12 g per liter to 18 g per liter and, in some embodiments, may be about 14 g per liter. The total sialic acid in the formulation may be between about 250 and about 1500 mg per liter and, in one embodiment, between about 300 and about 600 mg per liter. The formulation may contain one or a combination of the following sialic acid-containing protein components: (1) Up to 100% of the protein fraction from a whey protein concentrate, as commercially available from several sources including Davisco, New Zealand Milk, or Formost Farms, exhibiting about 20 – 30 mg sialic acid per gram of protein and, thus, contributing between about 140 and about 560 mg sialic acid per liter of formula; (2) up to 100% of the protein fraction from a nonfat dry milk product, as commercially available from several sources including New Zealand Milk, exhibiting about 2 – 10 mg sialic acid per gram protein and, thus, contributing between about 27 and about 139 mg sialic acid per liter of formula; (3) up to 6 g per liter of casein glycomacropeptide (cGMP) or related protein fraction, as commercially available from various sources, containing about 81% protein and between about 40 and about 300 mg sialic acid per gram of protein, but typically between about 40 and 60 mg SA/gm protein, and, thus, contributing between about 194 and about 1458 mg sialic acid per liter of formula, but typically between about 194 and 290 mg SA/liter of formula; and (4) up to about 6 g/liter of a cGMP fraction having an enhanced level of sialic acid.

**[00027]** When cGMP is employed, the casein glycomacropeptide may be extracted from milk using suitable processing. For example, the casein glycomacropeptide may be extracted from the retentate obtained from the concentration of whey protein. This may be done by at least partially removing lactose from the retentate and then adding ethanol to cause precipitation. The supernatant is then collected and dried to provide the casein glycomacropeptide. U.S. Patent No. 5,216,129, which is incorporated herein entirely by reference to the extent that it does not conflict with information described herein, provides a more detailed description of this process. Alternatively, the cGMP may be purchased from commercial sources such as, for example, The Tatua Co-Operative Dairy Company Limited, Tatuanui, Morrinsville, New Zealand, MD Foods Ingredients amba of DK-6920 Videbaek, Denmark or from DMV International of NCB-laan 80, NL-5460 BA Veghel, The Netherlands.

**[00028]** It has been found that a preferred type of cGMP that is useful for the present compositions and methods is a cGMP-based product having an enhanced concentration of sialic acid. As used herein, the terms "cGMP having an enhanced concentration of sialic acid" mean a casein glycomacropeptide (cGMP)-containing fraction of milk that has been treated to increase the level of sialic acid, and in which the level of sialic acid is higher, by any amount, than before the treatment. cGMP products with enhanced levels of sialic acid are described below in Examples 7 and 8.

**[00029]** One such product, an example of which is described in Example 7, can be referred to herein as "cGMP having an enhanced level of sialic acid", or "high-sialic acid cGMP". High-sialic acid cGMP has a sialic acid content of above about 60 mg/gm protein. It is preferred that the sialic acid content is above about 100 mg/gm protein, more preferred is above about 150 mg/gm protein, and yet more preferred is a sialic acid content of above 200 mg/gm protein. Typically, this product has a protein content of about 50% - 60% by weight for a dry powder product, a sialic acid content of about 190 – 230 mg/gm protein, or about 100 – 130 mg/gm powder. In

comparison, regular cGMP dry powder (for example, glycomacropeptide available from Tatua Co-Operative Dairy Company Limited) contains 81% protein by weight, and has a sialic acid content of about 52 mg/gm protein, or 42 mg/gm powder. It is apparent, therefore, that the sialic acid content of the high-sialic acid cGMP has been enhanced over that of the regular glycomacropeptide powder by about 3-fold on the basis of powder weight, and about 4-fold on the basis of protein content of the products. For comparison purposes, electrodialyzed (ED) whey powder contains about 14% protein on a dry basis, and contains about 30 mg of sialic acid/gm protein, or about 4.3 mg of sialic acid/gm of powder.

**[00030]** An advantage of using a high-sialic acid cGMP as a protein source in an infant formula is that the sialic acid content of the formula can be increased without replacing an undue amount of the conventional sources of protein that are used in the formula. This feature is useful in that it permits minimal disruption of the amino acid profile of the protein of the formula.

**[00031]** In a particular embodiment of a high-sialic acid cGMP, the product has a level of the amino acid threonine that is lower than the level of that amino acid in the glycomacropeptide from which the novel product is derived. As used herein, this type of high-sialic acid cGMP is referred to as "cGMP having an enhanced level of sialic acid and reduced threonine", or "high-sialic acid cGMP with reduced threonine". An example of this type of product is described below in Example 8.

**[00032]** High-sialic acid cGMP with reduced threonine has a sialic acid content of above about 60 mg/gm protein and a threonine concentration that is lower than about 15 gm/16 gm nitrogen. It is preferred that the sialic acid content is above about 100 mg/gm protein, more preferred is above about 150 mg/gm protein, and yet more preferred is a sialic acid content of above 200 mg/gm protein Typically, high-sialic acid cGMP with reduced threonine can have a sialic acid content of from about 85 to about 150 mg sialic acid (SA)/ gram of powder, preferably from about 90 to about 140 mg SA/g powder, which is comparable to the sialic acid content of

high-sialic acid cGMP. However, the threonine content of high-sialic acid cGMP with reduced threonine is only about one-fourth that of a commercial cGMP product. Preferably, the threonine content is below about 10 g/16 g nitrogen, more preferably below about 7 gm/16 gm nitrogen, even more preferably below about 5 g/16 g nitrogen, and yet more preferably below about 4 g/16 g nitrogen. Expressed in an alternative manner, the threonine content is below about 8% by weight of the total weight of amino acids of the protein, preferably below about 6%, more preferably below about 4%, and yet more preferably below about 3%.

**[00033]** An advantage provided by this type of enhanced sialic acid product is that in addition to the increase in sialic acid with reduced amino acid profile disruption, as discussed above, the threonine level of the protein sources in the infant formula can be minimized. This is desirable in some embodiments in order to reduce or eliminate the potential for hyperthreoninuria, or other disorder caused by, or exacerbated by, high levels of threonine in the diet.

**[00034]** By way of example, an infant formula of the present invention can be formulated to have a sialic acid content of at least 200 mg/liter and have a total protein content of between 12 and 16 grams/liter of which no more than 40% by weight is provided by a cGMP having an enhanced concentration of sialic acid. Preferably, such an infant formula has a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid, more preferably, the infant formula has a total protein content of between 13 and 15 grams/liter of which no more than 15% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

**[00035]** Also as an example, an infant formula of the present invention invention can be formulated to have a sialic acid content of at least 400 mg/liter and have a total protein content of between 13 and 15 grams/liter of which no more than 15% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

**[00036]** The following examples describe exemplary embodiments of the invention. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from consideration of the specification or practice of the invention as disclosed herein. It is intended that the specification, together with the examples, be considered to be exemplary only, with the scope and spirit of the invention being indicated by the claims which follow the examples. In the examples all percentages are given on a weight basis unless otherwise indicated.

## Example 1

**[00037]** This example illustrates the nutrient components in a commercial infant formula suitable for sialic acid addition for use in the present invention.

Table 1: Nutrient Information for Infant Formula (Enfamil® Lipil with Iron)

| **NUTRIENTS (Normal Dilution)** | **Per 100 Calories (5 fl oz)** |
|---|---|
| Protein, g | 2.1 |
| Fat, g | 5.3 |
| Carbohydrate, g | 10.9 |
| Water, g | 134 |
| Linoleic acid, mg | 860 |
| **Vitamins:** | |
| A, IU | 300 |
| D, IU | 60 |
| E, IU | 2 |
| K, µg | 8 |
| Thiamin (Vitamin B1), µg | 80 |
| Riboflavin (Vitamin B2), µg | 140 |
| B6, µg | 60 |
| B12, µg | 0.3 |
| Niacin, µg | 1000 |
| Folic acid (Folacin), µg | 16 |
| Pantothenic acid, µg | 500 |
| Biotin, µg | 3 |
| C (Ascorbic acid), mg | 12 |
| Choline, mg | 12 |
| Inositol, mg | 6 |
| **Minerals:** | |

| | |
|---|---|
| Calcium, mg | 78 |
| Phosphorus, mg | 53 |
| Magnesium, mg | 8 |
| Iron, mg | 1.8 |
| Zinc, mg | 1 |
| Manganese, µg | 15 |
| Copper, µg | 75 |
| Iodine, µg | 10 |
| Selenium, µg | 2.8 |
| Sodium, mg | 27 |
| Potassium, mg | 108 |
| Chloride, mg | 63 |

**[00038]** The ingredients of this particular formula are: reduced minerals whey, nonfat milk, vegetable oil (palm olein, soy, coconut, and high oleic sunflower oils), lactose, and less than 1%: mortierella alpina oil, crypthecodinium cohnii oil, vitamin A palmitate, vitamin D3, vitamin E acetate, vitamin K1, thiamin hydrochloride, vitamin B6 hydrochloride, vitamin B12, niacinamide, folic acid, calcium pantothenate, biotin, sodium ascorbate, inositol, calcium chloride, calcium phosphate, ferrous sulfate, zinc sulfate, manganese sulfate, cupric sulfate, sodium chloride, sodium citrate, potassium citrate, potassium hydroxide, sodium selenite, taurine, nucleotides (adenosine 5'-monophosphate, cytidine 5'-monophosphate, disodium guanosine 5'-monophosphate, disodium uridine 5'-monophosphate).

**[00039]** To use this particular formula to practice the present invention, it would be necessary to add, for example, from about 250 mg per liter to about 1500 mg per liter of sialic acid-containing ingredients to the composition described in Table 1. This added amount of sialic acid would be part of the total amount of protein (total protein of approximately 2.1 grams per 100 calories).

## Example 2

**[00040]** This example illustrates a particular protein source combination for a total sialic acid content of approximately 250 mg per liter. The

ingredients listed in Table 2 would be used to replace the protein component of the formula described in Table 1.

**[00041]** Table 2: Protein Source Composition A

| **Ingredient** | mg SA/ gm protein | % of protein in ingredient | g ingredient/ L | g protein/ L | mg SA/ L |
|---|---|---|---|---|---|
| Whey Protein Concentrate | 23.00 | 35.00 | 20.26 | 7.09 | 163.08 |
| Nonfat Dry Milk, Low Heat | 6.37 | 34.00 | 15.38 | 5.23 | 33.31 |
| cGMP | 52.00 | 81.00 | 1.45 | 1.17 | 61.07 |

Note: "SA" in table means sialic acid.

## Example 3

**[00042]** This example illustrates a particular protein source combination for a total sialic acid content of approximately 360 mg per liter. The ingredients listed in Table 3 replace the protein component of the formula described in Table 1.

**[00043]** Table 3: Protein Source Composition B

| **Ingredient** | mg SA/ gm protein | % of protein in ingredient | g ingredient/ L | g protein/ L | mg SA/ L |
|---|---|---|---|---|---|
| Whey Protein Concentrate | 23.00 | 35.00 | 37.00 | 12.95 | 297.85 |
| cGMP | 52.00 | 81.00 | 1.45 | 1.17 | 61.07 |

Note: "SA" in table means to sialic acid

## Example 4

**[00044]** This example illustrates a particular protein source combination for a total sialic acid content of approximately 600 mg per liter. The ingredients listed in Table 4 replace the protein component of the formula described in Table 1.

**[00045]** Table 4: Protein Source Composition B

| **Ingredient** | mg SA/ gm protein | % of protein in ingredient | g ingredient/ L | g protein/ L | mg SA/ L |
|---|---|---|---|---|---|
| Whey Protein Concentrate | 23.00 | 35.00 | 13.00 | 4.55 | 104.65 |

| | | | | | |
|---|---|---|---|---|---|
| cGMP | 52.00 | 81.00 | 12.00 | 9.72 | 505.44 |

Note: SA in table refers to sialic acid

## Example 5

**[00046]** Table 5 illustrates one possible complete nutritional formulation of an infant formula with a total sialic acid content of approximately 250 mg per liter.

**[00047]** Table 5: Exemplary infant formulation with sialic acid.

| Ingredient | Weight | Amount per 10000 liters |
|---|---|---|
| **Lactose (95% Solids)** | | **573.000 kg** |
| **Fat Blend** | | **332.500 kg** |
| **Whey Protein Concentrate (36% Protein, 5.8% Ash)** | | **202.578 kg** |
| **Nonfat Milk Solid (36% Prot., 52% CHO)** | | **153.844 kg** |
| **Caseino Glyco Macro Peptides (cGMP, 81.18% Prot.)** | | **14.500 kg** |
| **Mono-and Diglycerides** | | **7.233 kg** |
| **Calcium Phosphate, Tribasic** | | **6.520 kg** |
| **Single Cell Arachidonic Acid Oil** | | **6.485 kg** |
| **Dry Vitamin Premix for Enfamil AR Liquid** | | **5.250 kg** |
| Ascorbic Acid | 2924.250g | |
| Inositol | 834.750g | |
| Corn Syrup Solid | 654.938g | |
| Taurine | 582.750g | |
| Niacinamide | 119.438g | |
| Calcium Pantothenate | 44.730g | |
| Vitamin B12, 0.1% in Starch | 29.400g | |
| Biotin, 1% Trituration | 25.095g | |
| Thiamine Hydroxhloride | 13.913g | |
| Riboflavin | 10.238g | |
| Pyridoxine Hydrochloride | 8.138g | |
| Folic Acid | 2.363g | |
| **Lecithin Concentrate** | | **3.694 kg** |
| **Potassium Citrate** | | **3.350 kg** |
| **Single Cell Docosahexaenoic Acid Oil** | | **3.243 kg** |
| **Nucleotide Premix for Enfamil Powder** | | **2.900 kg** |
| Maltodextrin, 15 DE | 2552.290g | |
| Cytidine 5'-monophosphate, free acid | 202.710g | |
| Uridine 5'-monophosphate, disodium salt | 59.740g | |
| Adenosine 5'-monophosphate, free acid | 47.357g | |
| Guanosine 5'-monophosphate, disodium salt | 37.903g | |
| **Carrageenan** | | **2.826 kg** |
| **Magnesium Chloride** | | **1.657 kg** |
| **Calcium Chloride, Dihydrate** | | **1.200 kg** |
| **Choline Chloride** | | **0.700 kg** |
| **Ferrous Sulfate Heptahydrate** | | **0.682 kg** |
| **Sodium Citrate, Dihydrate, Granular** | | **0.455 kg** |
| **Trace Mineral Premix w/Selenite Trituration** | | **0.392 kg** |
| Zinc Sulfate, Monohydate | 276.238g | |
| Sodium Selenite Trituration, 0.5% | 65.907g | |
| Cupric Sulfate, powder | 29.510g | |
| Lactose, Grind A | 16.323g | |

| Ingredient | Weight | Amount per 10000 liters |
|---|---|---|
| Manganese Sulfate, monohydrate | 4.022g | |
| **Vitamin A,D,E,K Premix, Enfamil Liquid** | | **0.324 kg** |
| Tocopherol Acetate | 160.882g | |
| Soybean Oil | 139.612g | |
| Vitamin A Palmitate | 17.253g | |
| Cholecalciferol Concentrate | 5.715g | |
| Vitamin K1, Liquid | 0.538g | |
| **Ascorbic Acid** | | **0.150 kg** |
| **L-Carnitine** | | **0.150 kg** |
| **Water, Defluoridated, q.s. to** | | **10310.986 kg** |
| **Potassium Hydroxide** | | **---** |

**[00048]** Table 6 and Table 7 detail the content of specific components of the formulation described in Table 5 as a percentage of 1) weight to weight, 2) weight to volume, and 3) calories. The specific gravity of this particular formulation is 1.0310986.

**[00049]** Table 6: Infant formulation composition.

| Component | % w/w | % w/v |
|---|---|---|
| Protein | 1.38 | 1.42 |
| Fat | 3.50 | 3.61 |
| Carbohydrate | 7.20 | 7.43 |
| Ash | 0.37 | 0.38 |
| Total Solids | 12.45 | 12.84 |

**[00050]** Table 7: Infant formula caloric distribution

| Component | % |
|---|---|
| Protein | 8.38 |
| Fat | 47.83 |
| Carbohydrate | 43.79 |

## Example 6

**[00051]** Table 8 illustrates the nutritional content of the formulation presented in Example 5 per 100 calories, as well as per 100 milliliters of formula.

**[00052]** Table 8: Nutritional content of infant formulation.

| | Per 100 Cal | Per 100 ml |
|---|---|---|
| Calories, Cal | 100 | 68 |
| Protein, g | 2.1 | 1.42 |
| Fat, g | 5.3 | 3.6 |
| Carbohydrate, g | 10.9 | 7.4 |
| Linoleic Acid, mg | 860 | 580 |
| Linolenic Acid, mg | 80 | 54 |
| Arachidonic Acid, mg | 34 | 23 |
| Docosahexaenoic Acid, mg | 17 | 11.5 |
| | | |
| Vitamin A, IU | 300 | 200 |
| Vitamin D, IU | 60 | 41 |
| Vitamin E, IU | 2 | 1.35 |
| Vitamin K1, mcg | 12 | 8.1 |
| Thiamin, mcg | 120 | 81 |
| Riboflavin, mcg | 140 | 95 |
| Vitamin B6, mcg | 60 | 41 |
| Vitamin B12, mcg | 0.5 | 0.3 |
| Niacin, mcg | 1200 | 812 |
| Folic Acid, mcg | 16 | 10.8 |
| Pantothenic Acid, mcg | 500 | 340 |
| Biotin, mcg | 3 | 2 |
| Vitamin C, mg | 14 | 9.5 |
| Choline, mg | 12 | 8.1 |
| Inositol, mg | 6 | 4.1 |
| Taurine, mg | 6 | 4.1 |
| L-Carnitine, mg | 2 | 1.35 |
| | | |
| Calcium, mg | 78 | 53 |
| Phosphorus, mg | 53 | 36 |
| Magnesium, mg | 8 | 5.4 |
| Iron, mg | 1.8 | 1.2 |
| Zinc, mg | 1 | 0.68 |
| Manganese, mcg | 26 | 17.6 |
| Copper, mcg | 85 | 57 |
| Iodine, mcg | 15 | 10 |
| Sodium, mg | 27 | 18.3 |
| Potassium, mg | 108 | 73 |
| Chloride, mg | 63 | 43 |
| Selenium, mcg | 2.8 | 1.89 |
| Sialic acid, mg | 37 | 25 |
| | | |
| Calcium/Phosphorus Ratio | --- | --- |
| | | |
| AMP Equivalents, mg (a) | 0.5 | 0.34 |
| CMP Equivalents, mg (a) | 2.5 | 1.69 |
| GMP Equivalents, mg (a) | 0.3 | 0.20 |
| UMP Equivalents, mg (a) | 0.9 | 0.61 |
| Nucleotide Equivalents, mg (a) | 4.2 | 2.84 |
| TPAN-AMP, mg | -- | -- |
| TPAN-CMP, mg | -- | -- |
| TPAN-GMP, mg | -- | -- |
| TPAN-UMP, mg | -- | -- |
| Total TPAN, mg | -- | -- |
| TPAN-CMP/TPAN-GMP Ratio | -- | -- |

Note: Sum of the nucleotide and corresponding nucleoside expressed as the nucleotide weights.

## Example 7.

**[00053]** This illustrates the production of a cGMP product having enhanced levels of sialic acid.

**[00054]** A fraction of cheese whey that is enriched in GMP is fractionated by using anion chromatography to yield a fraction that is enhanced in sialic acid. This product exhibits an amino acid profile similar to that of currently commercially available GMP (available from Tatua Co-Operative Dairy Company Limited, Tatuanui, Morrinsville, New Zealand), but contains from 1.5 – 3 times the sialic acid content of currently available GMP products.

**[00055]** The sialic acid-enhanced fraction can be desalted, if desired, by electrodialysis, for example, and can be dried to yield a dry powder product, which is then useable for introduction into a liquid or a dry infant formula mix. This product is a high-sialic acid cGMP and is available as of the filing date of the present application from Tatua Co-Operative Dairy Company Limited, as products designated as X4738, X4739, X4740, and X4741. The protein content, sialic acid content, and amino acid profile of those materials is described in Table 9.

**[00056]** Table 9: Amino acid profile and sialic acid content of four examples of high-sialic acid cGMP products.

| Amino Acid | High-Sialic Acid cGMP Product Samples | | | | | | |
|---|---|---|---|---|---|---|---|
| | X4738 | X4739 | X4740 | X4741 | Average | cGMP Powder | ED Whey Powder |
| arginine | 1.22 | 0.96 | 0.69 | 0.7 | 0.89 | 1.4 | |
| histidine | 0.76 | 0.7 | 0.59 | 0.59 | 0.66 | 1 | |
| isoleucine | 10.36 | 8.42 | 11.28 | 11.51 | 10.39 | 11.6 | |
| leucine | 4 | 3.36 | 3.19 | 3.21 | 3.44 | 4.6 | |
| lysine | 7.48 | 7.91 | 6.89 | 7.08 | 7.34 | 8.3 | |
| methionine | 2 | 2.04 | 1.63 | 1.63 | 1.83 | 1.5 | |
| cystine | 0.21 | 0.47 | 0.13 | 0.09 | 0.23 | 0.2 | |
| phenylalanine | 1.54 | 5.88 | 1.96 | 2.08 | 2.87 | 1.8 | |
| tyrosine | 0.35 | 0.17 | 0.1 | 0.09 | 0.18 | 0.4 | |
| threonine | 13.13 | 15.16 | 17.18 | 17.57 | 15.76 | 15.9 | |
| tryptophan | 0 | 0 | 0 | 0 | 0.00 | 0 | |
| valine | 8.69 | 7.55 | 9.38 | 9.51 | 8.78 | 9.7 | |
| alanine | 6.8 | 6.58 | 6.41 | 6.53 | 6.58 | 6.6 | |
| aspartic acid | 10.61 | 12.12 | 9.93 | 10 | 10.67 | 11.1 | |
| glutamic acid | 22.91 | 24.23 | 23.28 | 23.14 | 23.39 | 26.2 | |
| glycine | 1.37 | 1.46 | 1.31 | 1.34 | 1.37 | 1.5 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| proline | 11.13 | 10.19 | 10.78 | 9.57 | 10.42 | 14.2 | |
| serine | 8.14 | 9.66 | 8.74 | 9.06 | 8.90 | 8.1 | |
| | | | | | | | |
| TOTAL | 110.7 | 116.86 | 113.47 | 113.7 | 113.68 | 124.1 | |
| | | | | | | | |
| | | | | | | | |
| % protein | 51.88 | 49.92 | 57.87 | 60.05 | 54.93 | 81 | 14.31 |
| mgSA/gm protein | 188.43 | 227.25 | 224.83 | 215.68 | 214.05 | 52 | 29.92 |
| mgSA/gm powder | 97.76 | 113.44 | 130.11 | 129.52 | 117.71 | 42.12 | 4.28 |
| Average | | | | | | | |
| | | | | | | | |
| Amino acid levels are expressed as grams of the amino acid per 16 grams of nitrogen. | | | | | | | |
| cGMP Powder is commercial glycomacropeptide from Tatua Co-Operative Dairy Company Ltd. | | | | | | | |
| ED Whey Powder is commercial electrodialyzed whey powder | | | | | | | |
| Samples X4738 – X4741 are samples of high-sialic acid cGMP available from Tatua Co-Operative Dairy Company Limited, Tatuanui, Morrinsville, New Zealand. | | | | | | | |

## Example 8.

**[00057]** This illustrates the production of a cGMP product having enhanced levels of sialic acid and low levels of threonine.

**[00058]** A fraction of cheese whey that is enriched in GMP is subjected to a partial proteolytic hydrolysis followed by fractionation by using anion chromatography to yield a fraction that is enhanced in sialic acid and has a low threonine content. This product contains from 1.5 – 3 times the sialic acid content of currently available GMP products, but the level of threonine is reduced to about one-fourth that of the starting GMP material.

**[00059]** The sialic acid-enhanced, low threonine fraction can be desalted, if desired, by electrodialysis, for example, and can be dried to yield a dry powder product, which is then useable for introduction into a liquid or a dry infant formula mix. This product is a high-sialic acid cGMP with reduced threonine and is available as of the filing date of the present application from Tatua Co-Operative Dairy Company Limited, Tatuanui, Morrisnville, New Zealand, as product designated as W4733. The protein content, sialic acid content, and amino acid profile of that material is described in Table 10.

**[00060]** Table 10: Amino acid profile and sialic acid content of high-sialic acid cGMP with reduced threonine.

| Amino Acid | High-Sialic Acid cGMP with Reduced Threonine | | |
|---|---|---|---|
| | W4733 | cGMP Powder | ED Whey Powder |
| arginine | 2.3 | 1.4 | |
| histidine | 0 | 1 | |
| isoleucine | 13.1 | 11.6 | |
| leucine | 5.3 | 4.6 | |
| lysine | 3.2 | 8.3 | |
| methionine | 0.7 | 1.5 | |
| cystine | 0.1 | 0.2 | |
| phenylalanine | 0 | 1.8 | |
| tyrosine | 0 | 0.4 | |
| threonine | 3.8 | 15.9 | |
| tryptophan | 0 | 0 | |
| valine | 16.3 | 9.7 | |
| alanine | 15.9 | 6.6 | |
| aspartic acid | 6.3 | 11.1 | |
| glutamic acid | 38.9 | 26.2 | |
| glycine | 2.5 | 1.5 | |
| proline | 16.9 | 14.2 | |
| serine | 0 | 8.1 | |
| | | | |
| TOTAL | 125.4 | 124.1 | |
| | | | |
| | | | |
| % protein | | 81 | 14.31 |
| mgSA/gm protein | | 52 | 29.92 |
| mgSA/gm powder | 138.03 | 42.12 | 4.28 |
| (Repeat analysis) | 117.02 | | |
| Average | 127.525 | | |
| | | | |
| Amino acid levels are expressed as grams of the amino acid per 16 grams of nitrogen | | | |
| cGMP Powder is commercial glycomacropeptide from Tatua Co-Operative Dairy Company Ltd. | | | |
| ED Whey Powder is commercial electrodialyzed whey powder | | | |
| Samples W4731, W4733, and W4735 are samples of enhanced sialic acid cGMP with reduced threonine available from Tatua Co-Operative Dairy Company Limited, Tatuanui, Morrinsville, New Zealand. | | | |

**[00061]** It is noted that the threonine level of the novel product are about one-fourth that of commercial cGMP. Accordingly, it is believed that use of

a high-sialic acid cGMP with reduced threonine in an infant formula can provide a formula having a high level of sialic acid at normal, desirable protein levels of about 14 g protein/ liter, and yet provide a desirable amino acid profile and low levels of threonine.

## Example 9.

**[00062]** This illustrates the use of a cGMP fraction having enhanced levels of sialic acid in an infant formula.

**[00063]** The cGMP product having enhanced levels of sialic acid can be used as a protein source in an infant formula in the same manner as a whey powder or normal cGMP powder. By way of example, Table 11 shows the sialic acid content that could be expected for an infant formula in which the protein content is supplied by conventional sources. The amount of cGMP powder that is used is limited in order to avoid undue deviation of the amino acid profile of the protein that is provided from a desirable infant standard profile.

**[00064]** Table 11: Sialic acid content of infant formula with protein provided by conventional sources:

| Protein Source | mg sialic acid/ gm protein | Percent protein | grams protein/liter | mg sialic acid/liter |
|---|---|---|---|---|
| Whey protein concentrate | 23 | 35% | 6.82 | 156.77 |
| Nonfat dry milk, low heat | 6.37 | 34% | 6.25 | 39.8 |
| cGMP Powder | 52 | 81% | 1.11 | 57.62 |
| Total | | | 14.17 | 254.18 |

**[00065]** The cGMP powder that is used in this formulation can be replaced by novel cGMP product having an enhanced level of sialic acid, as is described above in Example 7. Table 12 shows that when this is done, the sialic acid content of the formulation is more than doubled with no further disruption of the amino acid profile of the protein.

**[00066]** Table 12: Sialic acid content of infant formula with protein provided by conventional sources plus a cGMP product having an enhanced level of sialic acid:

| Protein Source | mg sialic acid/ gm protein | Percent protein | grams protein/liter | mg sialic acid/liter |
|---|---|---|---|---|
| Whey protein concentrate | 23 | 35% | 6.82 | 156.77 |
| Nonfat dry milk, low heat | 6.37 | 34% | 6.25 | 39.8 |
| cGMP Product with enhanced sialic acid | 214 | 54.93% | 1.11 | 237.54 |
| Total | | | 14.17 | 434.12 |

**[00067]** If the cGMP powder having enhanced sialic acid levels were to be used at double the levels described above at the expense of nonfat dry milk, the sialic acid content of the formula could be increased to the level shown in Table 13.

**[00068]** Table 13: Sialic acid content of infant formula with protein provided by conventional sources plus a cGMP product with an enhanced level of sialic acid:

| Protein Source | mg sialic acid/ gm protein | Percent protein | grams protein/liter | mg sialic acid/liter |
|---|---|---|---|---|
| Whey protein concentrate | 23 | 35% | 6.82 | 156.77 |
| Nonfat dry milk, low heat | 6.37 | 34% | 5.14 | 32.74 |
| cGMP Product with enhanced sialic acid | 214 | 54.93% | 2.22 | 475.08 |
| Total | | | 14.18 | 664.59 |

**[00069]** These and other modifications and variations to the present invention may be practiced by those of ordinary skill in the art, without departing from the spirit and scope of the present invention, which is more particularly set forth in the appended claims. In addition, it should be understood that aspects of the various embodiments might be interchanged both in whole and in part. Furthermore, those of ordinary skill in the art will appreciate that the foregoing description is by way of example only, and is not intended to limit the invention so further described in such appended claims. Therefore, the spirit and scope of the appended claims should not be limited to the description of the preferred versions contained therein.

**[00070]** All references cited in this specification, including without limitation all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification to the extent that they do not conflict with the disclosure of this specification. The discussion of the references herein is intended merely to summarize the assertions made by their authors and no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinency of the cited references.

What is claimed is:

1. An infant formula comprising cGMP having an enhanced concentration of sialic acid.

2. The infant formula according to claim 1, having a sialic acid level of at least about 200 mg/liter.

3. The infant formula according to claim 1, having a sialic acid level of at least about 250 mg/liter.

4. The infant formula according to claim 1, having a sialic acid level of at least about 300 mg/liter.

5. The infant formula according to claim 1, having a sialic acid level of at least about 400 mg/liter.

6. The infant formula according to claim 1, having a sialic acid level of at least about 600 mg/liter.

7. The infant formula according to claim 1, having a total protein content of between 12 and 16 grams/liter of which no more than 40% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

8. The infant formula according to claim 1, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

9. The infant formula according to claim 1, having a total protein content of between 13 and 15 grams/liter of which no more than 15% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

10. The infant formula according to claim 3, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

11. The infant formula according to claim 4, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by

weight is provided by a cGMP having an enhanced concentration of sialic acid.

12. The infant formula according to claim 5, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

13. The infant formula according to claim 1, wherein the cGMP having an enhanced concentration of sialic acid comprises high-sialic acid cGMP with reduced threonine.

14. The infant formula according to claim 13, having a sialic acid level of at least about 250 mg/liter.

15. The infant formula according to claim 13, having a sialic acid level of at least about 300 mg/liter.

16. The infant formula according to claim 13, having a sialic acid level of at least about 400 mg/liter.

17. The infant formula according to claim 13, having a sialic acid level of at least about 600 mg/liter.

18. The infant formula according to claim 13, having a total protein content of between 12 and 16 grams/liter of which no more than 40% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

19. The infant formula according to claim 13, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

20. The infant formula according to claim 13, having a total protein content of between 13 and 15 grams/liter of which no more than 15% by weight is provided by a cGMP having an enhanced concentration of sialic acid.

21. The infant formula according to claim 14, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration

of sialic acid and having a threonine content of not over 10 grams/16 grams nitrogen.

22. The infant formula according to claim 15, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid and having a threonine content of not over 7 grams/16 grams nitrogen.

23. The infant formula according to claim 16, having a total protein content of between 13 and 15 grams/liter of which no more than 30% by weight is provided by a cGMP having an enhanced concentration of sialic acid and having a threonine content of not over 4 grams/16 grams nitrogen.

24. The infant formula according to claim 13, having a total protein content of about 14 grams/liter of which not over 4% by weight is threonine and having a sialic acid content of at least 400 mg/liter.

25. A method of producing an infant formula comprising intermixing a cGMP having an enhanced concentration of sialic acid with sources of protein, carbohydrate and lipid sufficient to provide a nutritionally complete formula.