(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 February 2006 (23.02.2006)

PCT

(10) International Publication Number
WO 2006/019300 A2

(51) International Patent Classification: Not classified

(21) International Application Number:
PCT/NL2005/000609

(22) International Filing Date: 22 August 2005 (22.08.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04019856.6 20 August 2004 (20.08.2004) EP

(71) Applicant *(for all designated States except US)*: **N.V. NUTRICIA** [NL/NL]; Eerste Stationsstraat 186, NL-2712 HM Zoetermeer (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BEERMANN, Christopher** [DE/DE]; Bahnhofstrasse 120a, 61267 Neu-Anspach (DE). **BOEHM, Günther** [DE/DE]; Haselheckstrasse 1, 61209 Echzell (DE). **STAHL, Bernd** [DE/DE]; Breslauer Strasse 77, 61191 Rosbach (DE).

(74) Agent: **VAN WESTENBRUGGE, Andries et al.**; Nederlandsch Octrooibureau, P.O. Box 29720, NL-2502 LS The Hague (NL).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2006/019300 A2

(54) Title: INFANT FORMULA

(57) Abstract: The present invention relates to a nutritional composition containing protein, fat and carbohydrate; and a. a nucleotide component selected from the group consisting of nucleic acid, nucleic acid derivatives, nucleotides, nucleoside polyphosphates, polynucleotides, nucleosides, ribose, desoxyribose, and dinucleosidpolyphosphates (Np_XN); and b. a non-proteinaceous negatively charged, glycan or glycoconjugate component with a molecular weight between 200 and 20.000 dalton. The present nutritional composition is particularly suited for feeding infants as it mimics the protective effects of human milk, in particular against allergies and infections.

INFANT FORMULA

FIELD OF THE INVENTION

The present invention relates to a nutritional composition for feeding infants, containing fat, protein, carbohydrate, a nucleotide component and to the use thereof.

BACKGROUND OF THE INVENTION

Breastfeeding optimally supports the development of the infant and protects against infections and allergies. However, not all infants are in the position to receive human milk. It is therefore a continuing aim to provide infant formula, which simulates the functions of human milk. In addition to the desired compositional similarity between infant formula and human milk, it is also particularly desirable to mimic the protective effects of human milk, in particular protection against allergies and infections.

SUMMARY OF THE INVENTION

The present inventors have recognized that the molecular structure and density of charge of nucleotides is an important factor for the bioactivity of nucleotide components, particularly nucleotides. It was found that by combining nucleotide components with negatively charged non-protein components the bioactive effects of the nucleotide component in nutritional formulations may be enhanced significantly.

Hence, the present invention provides a nutritional composition containing a nucleotide component; and a non-proteinaceous negatively charged, glycan or glycoconjugate component with a molecular weight between 200 and 20.000 dalton (hereinafter referred to as NCC).

The present nutritional composition is particularly effective in:

- Enhancing immune cell proliferation, improving the development of T-lymphocyte sub populations, and enhancing the antibody response;
- Stimulating the development of the immune system of neonates

- Stimulating the development of the nerve system of neonates
- Stimulating the neonatal development and repair of the gastrointestinal tract after surgery or disease
- Modulating the gutflora, Stimulating the synthesis of long-chain polyunsaturated fatty acids
- Providing anti-infective, antibacterial/viral effects

Without wishing to be bound by theory, the improved activity is believed to be the result of an improved presentation and delivery of the negatively charged nucleotide component to the epithelial cells, due to interaction of the NCC and the nucleotide component e.g. via hydrogen and salt bridges. The biological active molecular anionic charge of nucleotides is condensed and the molecular distribution of charge is beneficially altered.

The present nutritional composition can be even further improved by combining the nucleotide component and NCC with bivalent cations, preferably calcium and/or zinc. The cation will increase proximity of the nucleotide component and the NCC in a liquid environment (e.g. the intestinal tract) by formation of hydrogen/salt bridges, thereby further increasing the interactive effects between the NCC and the nucleotide components.

DETAILED DESCRIPTION

The present invention provides a nutritional composition containing protein, fat and carbohydrate; and a nucleotide component selected from the group consisting of nucleic acid, nucleic acid derivatives, nucleotides, nucleoside polyphosphates, polynucleotides, nucleosides, ribose, desoxyribose, and dinucleosidpolyphosphates (Np_xN); and a non-proteinaceous negatively charged, glycan or glycoconjugate component with a molecular weight between 200 and 20.000 dalton

Nucleotide component

The present composition contains a nucleotide component selected from the group consisting of nucleic acid, nucleic acid derivatives, nucleotides, nucleoside polyphosphates, polynucleotides, nucleosides, ribose, desoxyribose, and dinucleosidpolyphosphates (Np_xN).

Nucleic acids are typically heterocyclic pyrimidine bases cytosine, thymine, uridine and derivatives, like pseudouridine, dihyderouridine, ribothymidine, 4-thiouridine, 3-methylcytidine, N-acetylcytidine, lysidine as well as purine bases adenine and guanosine and derivatives, like 1-methyladenosine, N6-isopentenyladenosine, inosine, N7-methylguansine, N2-dimethylguanosine and wyosine. Nucleosides such as N-glycoside are pyrimidine or purine base glycoconjugates. Preferred nucleotides are phosphoesters of nucleosides, which are monomers or polymers in the form of oligo- or polynucleotides. For this application especially hydrolysates of desoxyribonucleic acid and ribonucleic acid, t-ribonucleic acid and ribosomes derived from animal milk, animal and plant tissues, yeasts, bifido- and lactobacteria and synthetic molecules are suitable raw material sources. (Biochemistry, Donald Voet and Judith G. Voet, John Wiley and Sons, Inc NY second edition chapter 28, pp 849)

Preferably, the present composition contains at least one, preferably at least two, even more preferably at least three nucleotides selected from the group consisting of cytidine monophosphate (CMP), guanosine monophosphate (GMP), adenosine monophosphate (AMP), uridine monophosphate (UMP), and inosine monophosphate (IMP).

In a further preferred embodiment the present composition contains ribose as a nucleotide component, preferably D-ribose. D(-)Ribose is a pentose sugar that can be purchased as crystalline product. Ribose is a main constituent of nucleic acids. Preferably the present composition contains between 0.01 wt.% and 50 wt.% ribose based on dry weight of the product, more preferably between 0.05 and 10 wt.%, even more prefferably between 0.5 and 10 wt.%

The present composition preferably comprises between 5 and 100 mg nucleosides and/or between 5 and 100 mg nucleotides per 100 gram dry weight of the composition, more preferably between 5 and 50 mg. The nucleotides and/or

nucleosides further stimulate the immune system, acting synergistically with the NCC of the present composition.

Negatively charged component (NCC)

The present composition contains a negatively charged non-proteineous glycan and glycoconjugate component (NCC) with a molecular weight between 200 and 20.000 dalton.

The NCC is negatively charged in water with a pH of 7. The negative charge is preferably provided by a carboxylic, phosphate and/or sulphate group, most preferably by a carboxylic group. Preferably the NCC has a MW between 1000 and 10.000 Dalton. The weight ratio nucleotide component/NCC in the present nutritional composition is preferably between 100 and 0.1.

Preferably the NCC is selected from the group consisting of glycosphingolipids, acid oligosaccharides, and sialysated oligosaccharides. Preferably the sialysated oligosaccharides is sialyllactose and/or disialo-lactoneotertaose (DS-LNT). Glycosphingolipids are typically compounds with a monosaccharide attached directly to a ceramide.

Preferably the NCC contains a ganglioside (a glycosphingolipid). Gangliosides are typically highly complex oligoglycosylceramides, which contain one or more sialic acid groups (*N*-acyl, especially acetyl, derivatives of neuraminic acid, abbreviated to "NANA") in addition to glucose, galactose and galactosamine. For this application, especially buttermilk, egg yolk lecithin are suitable raw material sources of gangliosides. (Biochemistry, Donald Voet and Judith G. Voet, John Wiley and Sons, Inc NY second edition chapter 23). Hence the present composition preferably contains egg yolk lecithin and/or buttermilk.

In a particularly preferred embodiment the present composition contains a ganglioside selected from the group consisting GM3, GM1 and GD1.

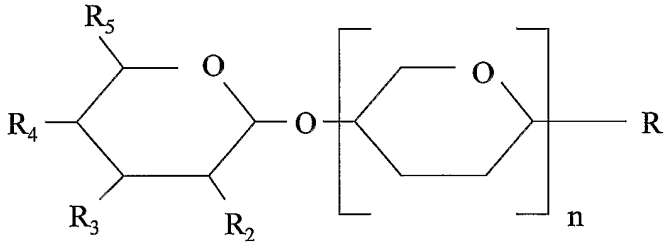
In a further preferred embodiment, the present composition contains sulfoglycosphingolipids as the NCC. Sulfoglycosphingolipids are sulfate esters of

galactosylceramide and lactosylceramide (often referred as "sulfatides" or "lipid sulfates"), with a sulfate group linked to position 3 of the galactosyl moiety.

Acidic oligosaccharides

The present composition preferably includes acidic oligosaccharides with a DP from 2 to 100, preferably from 2 to 60. The term acid or acidic oligosaccharide refers to oligosaccharides comprising at least one acidic group selected from the group consisting of N-acetylneuraminic acid, N-glycoloylneuraminic acid, free or esterified carboxylic acid, sulfuric acid group and phosphoric acid group. The acidic oligosaccharide preferably comprises uronic acid units (i.e. uronic acid polymer), more preferably galacturonic acid units. The present composition preferably contains between 0.1 and 10 grams acid oligosaccharides per 100 gram dry weight of the present composition, more preferably between 1 and 6 grams per 100 gram dry weight.

Structure I: Polymeric acid oligosaccharide



wherein:

R is preferably selected from the group consisting of hydrogen, hydroxy or acid group, preferably hydroxy; and at least one selected from the group consisting of R2, R3, R4 and R5 represents N-acetylneuraminic acid, N-glycoloylneuraminic acid, free or esterified carboxylic acid, sulfuric acid group and phosphoric acid group, and the remaining of R2, R3, R4 and R5 representing hydroxy and/or hydrogen. Preferably one selected from the group consisting of R2, R3, R4 and R5 represents N-acetylneuraminic acid, N-glycoloylneuraminic acid, free or

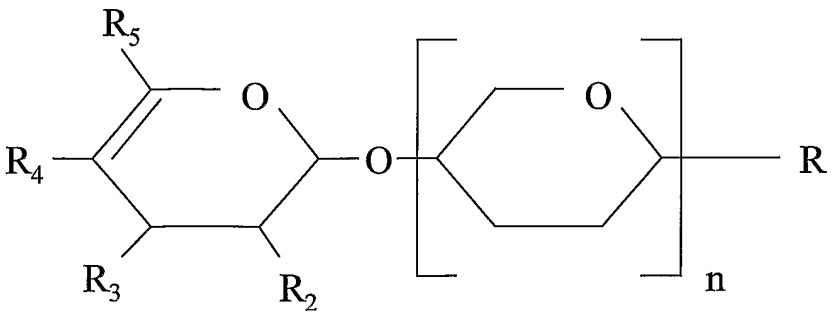
esterified carboxylic acid, sulfuric acid group or phosphoric acid group, and the remaining represent hydroxy and/or hydrogen. Even more preferably one selected from the group consisting of R2, R3, R4 and R5 represents free or esterified carboxylic acid and the remaining of R2, R3, R4 and R5 representing hydroxy and/or hydrogen; and n is an integer and refers to a number of hexose units (see also Degree of Polymerisation, below), which may be any hexose unit. Suitably n is an integer between 1-5000. Preferably the hexose unit(s) is a uronic acid unit.

Most preferably R1, R2 and R3 represent hydroxy, R4 represent hydrogen, R5 represents carboxylic acid, n is any number between 1 and 250, preferably between 1 and 10 and the hexose unit is galacturonic acid.

The detection, measurement and analyses of the preferred acid oligosaccharides as used in the present method are given in applicants earlier patent application relating to acid oligosaccharides, i.e. WO 0/160378.

Preferably, the acid oligosaccharide has one, preferably two, terminal uronic acid units, which may be free or esterified. Preferably the terminal uronic acid unit is selected from the group consisting of galacturonic acid, glucuronic acid, guluronic acid, iduronic acid, mannuronic acid, riburonic acid and alturonic acid. These units may be free or esterified. In an even more preferred embodiment, the terminal hexose unit has a double bond, which is preferably situated between the C4 and C5 position of the terminal hexose unit. Preferably one of the terminal hexose units comprises the double bond. The terminal hexose (e.g. uronic acid) preferably has a structure according to Fig.2.

Fig. 2: Preferred terminal hexose acid group



wherein;

R is preferably selected from the group consisting of hydrogen, hydroxy or acid group, preferably hydroxy (see above); and at least one selected from the group consisting of R2, R3, R4 and R5 represents N-acetylneuraminic acid, N-glycoloylneuraminic acid, free or esterified carboxylic acid, sulfuric acid group and phosphoric acid group, and the remaining of R2, R3, R4 and R5 representing hydroxy and/or hydrogen. Preferably one selected from the group consisting of R2, R3, R4 and R5 represents N-acetylneuraminic acid, N-glycoloylneuraminic acid, free or esterified carboxylic acid, sulfuric acid group and phosphoric acid group, and the remaining of R2, R3, R4 and R5 represent hydroxy and/or hydrogen. Even more preferably one selected from the group consisting of R2, R3, R4 and R5 represents free or esterified carboxylic acid and the remaining of R2, R3, R4 and R5 represent hydroxy and/or hydrogen; and n is an integer and refers to a number of hexose units (see also Degree of Polymerisation, below), which may be any hexose unit. Suitably n is an integer between 1-100 representing the number of hexose units said hexose units preferably being uronic acid, even more preferably being galacturonic acid units. The carboxylic acid groups on these units may be free or (partly) esterified, and are preferably at least partly methylated.

Most preferably, R2 and R3 represent hydroxy, R4 represent hydrogen and R5 represents free or esterified carboxylic acid.

The acid oligosaccharides used in the invention are preferably prepared from pectin, pectate, alginate, chondroitine, hyaluronic acids, heparine, heparane, bacterial carbohydrates, sialoglycans, fucoidan, fucooligosaccharides or carrageenan, more preferably from pectin and/or alginate. Preferably pectin, often biochemically depolymerized is used. Most preferably pectin depolymerized with pectin lyase is used.

Bivalent cation

The present nutritional composition preferably contains a bivalent cation. The bivalent cation enhances proximity of the nucleotide component and the NCC, further modifying the charge density and improving biological activity. Preferably the present composition contains at least one bivalent cation selected from the group consisting of magnesium, calcium, iron, chromium, manganese, molybdenum, copper and zinc. Preferably the present composition contains at least calcium and/or zinc.

Zinc is advantageously included in the present composition. Zinc enhances the biological activity of the nucleotides when combined with the present NCC, and also s an essential micronutrient for growth and development of the immune function, particularly for infants. Zinc deficiency impairs overall immune function and resistance to infection. Hence, the present composition advantageously comprises zinc, preferably in an amount of 2 to 100 mg zinc per 100 gram dry weight of the present composition, even more preferably between 3 and 25 mg zinc per 100 g dry weight of the present composition. The weight of zinc is calculated as elementary zinc.

In a further preferred embodiment, the present composition contains calcium for improved charge interaction. Calcium is also essential in an infants diet, and hence advantageously included in the present composition. Preferably the present composition contains between 150 and 1000 mg calcium by weight total dry weight of the composition.

Macronutrients

The present composition can be advantageously used as an infant formula,. The infant formula preferably administered to the infant in liquid form. The term infant includes weaning infants, and toddlers.

In a preferred embodiment the present invention relates to an nutritional composition which provides the macronutrients of the infant diet. Hence, the present composition preferably contains 30 to 60 en% lipid; 5 to 15 en% protein; and 25 to 65 en% carbohydrate. Preferably, the present composition contains 43 to

53 en% lipid; 7 to 11 en% protein; and 43 to 53 en% carbohydrate (en% is short for energy percentage and represents the relative amount each constituent contributes to the total caloric value of the preparation). The term "protein" or protein component in this context is the cumulative of protein, polypeptides, peptides and amino acids. The carbohydrate in the present composition is preferably provided largely by lactose, i.e. preferably at least 75 wt.% of total digestible carbohydrate is provided by lactose, preferably at least 90 wt.%.

Essential fatty acids content

The present composition preferably contains at least 10 wt.% linoleic acid (LA) based on total fatty acids, preferably between 11 and 20 wt.%, more preferably between 12 and 15 wt.%. The present composition preferably contains at least 1 wt.% alpha linolenic acid (ALA) based on total fatty acids, preferably between 1.5 and 4 wt.% ALA, even more preferably between 2 and 2.5 wt.%. To reduce intestinal stress, the weight ratio LA/ALA is preferably between 2 and 10, preferably between 5 and 7.5. The present composition preferably includes between 0.05 and 5 wt% gamma-linolenic acid (GLA) based on total fatty acids, preferably between 0.1 and 1 wt.%. Preferably the present composition contains between 0.05 and 5 wt% steraidonic acid (STA) preferably more preferably between 0.1 and 1 wt.%.

Long chain-polyunsaturated fatty acid content

The present composition preferably comprises at least one long chain-polyunsaturated fatty acid with 20 or 22 carbon atoms (LCPUFA) in an amount exceeding 0.1 wt.% based on total fatty acids, selected from the group consisting of docosahexaenoic acid (DHA), arachidonic acid (AA) and eicosapentaenoic acid (EPA). Preferably the composition contains DHA in an amount exceeding 0.1 wt.% based on total fatty acids; and AA in an amount exceeding 0.1 wt.% based on total fatty acids.

Preferably at least one LCPUFA of this group is included in an amount between 0.15 and 1 wt.% based on total fatty acid content of the composition. Preferably at least two of these LCPUFA's are present in an amount of between 0.15 and 1 wt.%

based on total fatty acid content of the composition. Preferably the composition contains AA and DHA, even more preferably AA, DHA and EPA.

The AA content preferably does not exceed 5 wt.%, more preferably does not exceed 1 wt.%, most preferably between 0.1 and 0.6 wt.% of the total fatty acids. In the present composition, EPA and/or DHA are advantageously added to balance the action of AA, e.g. reduce the potential pro-inflammatory action of AA metabolites. Excess metabolites from AA may cause inflammation. Hence, the present composition preferably comprises AA, EPA and/or DHA, wherein the weight ratio AA/DHA preferably is above 0.25, preferably above 0.5, even more preferably above 1. The ratio AA/DHA is preferably below 25, preferably below 10. The weight ratio AA/EPA is preferably between 1 and 100, more preferably between 5 and 20. The weight ratio EPA/DHA is preferably 1 or lower, more preferably below 0.5.

In a preferred embodiment, the content of LCPUFA does not exceed 3 wt.% of the total fatty acids as it is desirable to mimic human milk as closely as possible. For the same reason, the present composition preferably contains less than 1 gram omega-3 LCPUFA per 100 gram fatty acids, more preferably between 0.1 and 0.75 gram per 100 gram fatty acids. The omega-6 LCPUFA content preferably does not exceed 2 gram per 100 gram fatty acids and is preferably between 0.1 and 0.75 gram per 100 gram fatty acids.

The LCPUFAs and the other fatty acids may be provided as free fatty acids, in triglyceride form, in phospholipid form, or as a mixture of one of more of the above. The present composition advantageously comprises at least one of AA and DHA in phospholipid form, as these reduce the incidence of inflammatory disorders of the intestine. The present composition preferably comprises between 0.1 and 5 mg AA from phospholipid per gram total fat and between 0.1 and 5 mg DHA from phospholipid per gram total fat. Preferably the AA and/or DHA are at least partly present in the form of phosphatidylcholine (PC) and/or phosphatidylethanolamine (PE), e.g. AA and/or DHA containing PE and/or PC.

Oligosaccharides

The present composition preferably comprises indigestible oligosaccharides with a degree of polymerisation (DP) of between 2 and 100. The oligosaccharides are believed to be important for providing a suitable intestinal environment for improved presentation and charge density of the combination of nucleotide component and NCC. The indigestible oligosaccharides reduce the pH of the intestinal environment, improving biological activity of the nucleotides. Preferably, the present composition contains 0.1 to 12 grams indigestible oligosaccharides per 100 gram dry weight of the composition, preferably between 3 and 8 grams, more preferably between 5 and 7.5 grams. After reconstitution of the powder in liquid and administration of the liquid formula to the infant, these amounts of indigestible oligosaccharides provide the desired effects without causing intestinal discomfort. Suitable indigestible oligosaccharides are not or only partially digested in the intestine by the action of acids or digestive enzymes present in the human upper digestive tract (small intestine and stomach), but are fermentable by the human intestinal flora. The oligosaccharides are preferably water-soluble (exceeding a solubility of 1 gram oligosaccharide per liter water). The average DP of the present oligosaccharide is preferably below 40, even more preferably below 20. Optimally, the present composition comprises between 2 and 12 grams oligosaccharides with a DP of 2 to 60, more preferably with a DP of 2 to 10 (i.e. the sum of the weights of those oligosaccharides with a DP of 2, 3, 4, 5, 6, 7, 8, 9 and 10).

According to a further embodiment at least one of the oligosaccharides of the present composition is selected from the group consisting of inulin, fructooligosaccharides, indigestible dextrins, galactooligosaccharides (including transgalactooligosaccharides), xylooligosaccharides, arabinooligosaccharides, glucooligosaccharides, mannooligo-saccharides, lacto-N-neotetraose, fucooligosaccharides (containing at least one fucose saccharide unit), acidic oligosaccharides (e.g. uronic acid oligosaccharides such as pectin oligosaccharides) and mixtures thereof.

Preferably, the present composition comprises at least one selected from the group consisting of inulins and fructooligosaccharides and at least one selected from the group consisting of galactooligosaccharides (including

transgalactooligosaccharides) and pectin hydrolysate. In a particularly preferred embodiment, the present composition comprises 2 to 12 grams oligosaccharides with a DP of 2 to 10 and β-linked galactose and glucose saccharides, more preferably transgalactooligosaccharides (i.e. $[gal]_n$ -glu, wherein n is 2 to 10). In a particularly preferred embodiment, the present composition comprises transgalactooligosaccharides (i.e. $[gal]_n$ -glu, wherein n is 2 to 10), pectin hydrolysate and at least one selected from the group consisting of fructooligosaccharides and inulin. The present oligosaccharide is preferably derived from animal milk, a mixture of oligosaccharides derived from animal milk or a fucosylated oligosaccharide (oligosaccharide containing at least one fucose saccharide unit).

For further improvement of gut maturation over the whole area of the colon, preferably at least 10 wt.% of the oligosaccharides in the present composition has a DP of 2 to 5 (i.e. 2, 3, 4 and/or 5) and at least 5 wt.% has a DP of 10 to 100. Preferably at least 50 wt.%, more preferably at least 75 wt.% of the oligosaccharides have a DP of 2 to 10 (i.e. 2, 3, 4, 5, 6, 7, 8, 9 and/or 10), because these are believed to work throughout the ileum and proximal and middle parts of the colon and because the weight percentage of oligosaccharides that needs to be incorporated in the composition to achieve the desired effect is reduced.

Preferably, the weight ratios:

(oligosaccharides with DP 2 to 5) : (oligosaccharides with DP 6 to 9); and

(oligosaccharides with DP 10 to 100) : (oligosaccharides with DP 6 to 9)

are both above 1. Preferably both weight ratios are above 2, even more preferably above 5.

The present composition preferably comprises 0.5 to 10 gram galactooligosaccharide with DP between 2 and 10 per 100 gram dry weight of the composition, more preferably between 1 and 5 gram. The preferred galactooligosaccharides is transgalactooligosaccharide, as this best mimics human milk oligosaccharides. The present invention preferably comprises 0.5 to 10 gram fructopolysaccharide with DP between 10 and 60 per 100 gram dry weight of the composition, more preferably between 1 and 5 gram. The term

"fructopolysaccharide" refers to a polysaccharide carbohydrate comprising a chain of at least 10 β-linked fructose units.

Liquid

The present nutritional composition is preferably in powder or liquid form or in tablet form, wherein said tablet has a weight between 5 and 25 grams. Preferably, the present composition is provided in powered form as this increases shelf life. The present composition is preferably administered orally in liquid form. Prior to the administration of the present composition, it is preferably admixed with a liquid, preferably water.

Stool irregularities (e.g. hard stools, insufficient stool volume, diarrhea) is a major problem in many babies and ill subjects that receive liquid foods. It was found that stool problems may be reduced by administering the present composition in liquid form, having an osmolality between 50 and 500 mOsm/kg, more preferably between 100 and 400 mOsm/kg, most preferably between 220 and 300 mOsm/kg.

In view of the above diarrhea problem, it is also important that the liquid food does not have an excessive caloric density as this causes significant intestinal stress. However, the formula needs to provide sufficient calories to feed the infant. Hence, the liquid food preferably has a caloric density between 0.5 and 0.9 kcal/ml, preferably between 0.6 and 0.8 kcal/ml.

Application

The present composition is advantageously administered to infants with the age between 0 and 2 years. The present composition can also be advantageously used in a method for providing the nutritional requirements of a premature infant (an infant born before 37 weeks gestation). In a preferred embodiment, the present invention provides a method for feeding infants with an age between 0 and 30 day.

The present composition can be advantageously used to treat or prevent diseases wherein a comprised immune system and/or intestinal barrier immaturity is underlying the development of the course of the disease. The present composition can thus be advantageously used to treat or prevent diarrhea or allergy, particularly in infants with an age between 0 and 2. The present composition is particularly

suitable for the treatment and/or prevention of allergic rhinitis, allergic conjunctivitis, allergic dermatitis, atopic dermatitis and/or food allergy. In a preferred embodiment, the present method provides for a method for the treatment and/or prevention of infections, said method comprising administering the present composition.

The invention is further illustrated by means of the following examples:

Example 1: Infant nutrition

A liquid infant nutrition, prepared by admixing 13.9 g powder with water to yield 100 ml final product, said liquid product comprising per 100 ml:

Energy: 66 kcal

Protein: 8 en%

1.3 g (containing 0.6 g casein; 0.8 g whey; 0.072 g L-arginine)

Digestible carbohydrates: 44 en%

7.4 g (containing 7.3 g lactose)

Fat: 48 en%

3.5 g (containing 0.41 g linoleic acid ; 0.08 g α-linolenic acid; 0.012 g arachidonic acid; 0.002 g eicosapentanoic acid; 0.006 g docosahexaenoic acid; 1.4 g oleic acid;)

Fibre:

0.8 g (containing 0.05 g fructopolysaccharide (Raftiline HP™, Orafti, Tienen, Belgium); 0.55 g transgalactooligosaccharides (Vivinal-GOS™ (Borculo Domo Ingredients, Netherlands); 0.20 g pectin hydrolysate prepared as described in EP1373543, example 1.

Nucleotide components:

0.89 mg	Cytidine-5-monophosphate;
0.55 mg	Uridine-5-monophosphate;
0.82 mg	Adenosine-5-monophosphate;
0.20 mg	Guanosine-5-monophosphate;
0.34 mg	Inosine-5monophosphate.

NCC:

5 mg GM3, 50 mg pectin derived oligosaccharides with DP between 5 and 50, and 20 mg sialyllactose

Calcium:

53 mg calcium

Zinc:

0.8 mg zinc

Osmolarity: 300 mOsmol/l

The composition further contains choline (6 mg/100 ml) and taurine (6.3 mg/100 ml); minerals and trace elements and vitamins in amounts in compliance with the international guidelines for infant milk formula.

Example 2:

Composition according to example 1, wherein the nucleotide component is replaced by dinucleosidpolyphosphates (NpxN) Gp4G

Example 3:

Composition according to example 1, wherein the nucleotide component is an DNA/RNA oligomers extract

Example 4

Composition according to example 1, comprising 1 wt.% D-ribose based on total dry weight of the composition.

CLAIMS

1. Nutritional composition containing protein, fat and carbohydrate; and

a. a nucleotide component selected from the group consisting of nucleic acid, nucleic acid derivatives, nucleotides, nucleoside polyphosphates, polynucleotides, nucleosides, ribose, desoxyribose, and dinucleosidpolyphosphates (Np_xN); and

b. a non-proteinaceous negatively charged, glycan or glycoconjugate component with a molecular weight between 200 and 20.000 dalton.

2. Nutritional composition according to claim 1, wherein component b. has a molecular weight between 1000 and 10.000 dalton.

3. Nutritional composition according to claim 1 or 2, wherein the nutritional composition contains 5 to 15 en% protein; 30 to 60 en% fat; and 25 to 65 en% carbohydrate.

4. Nutritional composition according to any one of the preceding claims, wherein the nutritional composition comprises between 5 and 100 mg nucleotides and/or between 5 and 100 mg nucleosides per 100 gram dry weight of the composition.

5. Nutritional composition according to any one of claims 1-3, wherein the nucleotide component is ribose.

6. Nutritional composition according to any one of the preceding claims containing between 150 and 1000 mg calcium and/or 2 to 100 mg zinc, each per 100 gram dry weight of the present composition.

7. Nutritional composition according to any one of the preceding claims wherein the negatively charged component is selected from the group consisting of acidic oligosaccharides and gangliosides.

8. Nutritional composition according to any one of the preceding claims, wherein the negatively charged component is a polygalacturonic acid with a DP between 2 and 100, preferably pectin hydrolysate.

9. Nutritional composition according to any one of claims 1-7, wherein the negatively charged component is a ganglioside.

10. Nutritional composition according to any one of the preceding claimsfor use as a medicament.

11. Use of a nutritional composition according to any one of claims 1-9, for the manufacture of a composition for use in a method for providing nutrition to an infant, said method comprising administering the nutritional composition

12. Use of a nutritional composition as defined in anyone of claims 1 - 9 for the manufacture of a composition for administration to a mammal for the treatment and/or prevention of an inflammatory disease, diarrhea, eczema and/or atopic dermatitis.

13. Use according to claim 12, wherein the inflammatory disease is allergy.

14. Use according to any one of claims 12 or 13, wherein the mammal is a human infant.