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(54) Title: METHOD FOR REDUCING THE OCCURRENCE OF INFECTION IN YOUNG CHILDREN

(57) Abstract: The invention pertains to the use of a composition in reducing the number of infections episodes and the occurrence of infections in young children, said composition comprising: (a) long chain polyunsaturated fatty acids, wherein the amount of arachidonic acid is less than 0.06 gram per 100 gram fatty acid; and comprising, per 100 g fatty acids: (i) 0.3-0.6 gram docosahexaenoic acid; (ii) 0.2-0.4 gram eicosapentaenoic acid; and (b)between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising: (i) 1.4-2 gram short-chain galactooligosaccharides; and (ii) 0.1 -0.5 gram long-chain fructopolysaccharides.

Method for reducing the occurrence of infection in young children

The invention is in the field of reducing the occurrence of infection in young children and/or reducing the number of infectious episodes in young children.

BACKGROUND DESCRIPTION

Blood levels of docosahexaenoic acid (DHA) and arachidonic acid (ARA) are typically higher in breast-fed infants than in infants fed formulas not containing these fatty acids. For these reasons, infant formula manufacturers and consumers are interested in providing DHA and ARA directly to infants. According to standing recommendations, infant formula should be supplemented with ARA in amounts at least equal to the amounts of DHA.

WO 2005/122790 discloses a composition comprising oligosaccharides and long-chain polyunsaturated fatty acids (LC-PUFAs) for improving intestinal barrier integrity. The LC-PUFAs involve a combination of DHA, eicosapentaenoic acid (EPA) and ARA, wherein ARA was found to be particularly effective in reducing tight junction permeability, and its thus favored in relatively high amounts, preferably at least 0.1 wt% ARA of the total fat.

WO 2006/022543 discloses a combination of oligosaccharides and immunoglobulins to treat infections. The combination may be incorporated in an infant formula further comprising LC-PUFAs, wherein it is believed that ARA, DHA and EPA act synergistically with the oligosaccharides. High amounts of ARA are advocated. WO 2006/115412 teaches similarly.

SUMMARY OF THE INVENTION

The inventors have observed in a clinical study with young children that by administering a specific formula the number of infections episodes and the occurrence of infections in young children are significantly reduced. A summary of the study is enclosed. The percentage of young children that suffered from infectious episodes decreased significantly when administered a formula enriched with specific

oligosaccharides and a LCPUFA composition comprising insignificant amounts of ARA.

In view of the art, it is surprising that these results are obtained in young children. For example, many benefits have been ascribed to compositions comprising ARA in the art. However, the present composition has a low ARA content. Additionally, it is surprising that the benefits were observed in a subpopulation which already consumes a variety of foodstuff, and only a relatively small part of the diets being provided by a growing up milk with present constitutes and amounts. It is particularly difficult to predict the effect of mixture of ingredients in young children.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a pharmaceutical or nutritional composition for use in the treatment and/or prevention of infections in young children; reducing the occurrence of infection in young children and/or reducing the number of infectious episodes in young children, said composition comprising:

a) long chain polyunsaturated fatty acids (LC-PUFAs) with 20 and 22 carbon atoms, wherein the amount of arachidonic acid (ARA) is less than 0.06 gram per 100 gram fatty acid; and comprising:
   (i) 0.3-0.6 gram docosahexaenoic acid (DHA, n-3) per 100 g fatty acids; and
   (ii) 0.2-0.4 gram eicosapentaenoic acid (EPA, n-3) per 100 g fatty acids;
b) between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:
   (i) 1.4-2 gram galactooligosaccharides with a degree of polymerization of 2 – 7; and
   (ii) 0.1 - 0.5 gram fructopolysaccharides with degree of polymerization of 2 - 150.

Worded differently, the present invention provides a method for the treatment and/or prevention of infections; reducing the occurrence of infection; and/or reducing the number of infectious episodes, by administering the composition as characterized herein to a young child .

The invention also pertains to the use of a composition characterized herein in the manufacture of a (pharmaceutical or nutritional) composition for the treatment and/or prevention of infections in young children; reducing the occurrence of infection; and/or reducing the number of infectious episodes in young children.

Polyunsaturated fatty acids

The present inventors surprisingly found that eicosapentaenoic acid (EPA, 20:5 n-3) and docosahexaenoic acid (DHA, 22:6 n-3), particularly DHA, in significant absence/very limited amount of ARA, and in combination with the specified oligosaccharides effectively aids in reducing the occurrence and severity of infections and the number of infectious episodes.

The present inventors found that lower concentrations of LC-PUFAs were effective in reducing the occurrence and severity of infections. Hence, the content of LC-PUFA with 20 and 22 carbon atoms in the present composition, preferably does not exceed 2.0 wt% of the total fat content, more preferably does not exceed 1.5 wt%, even more preferably does not exceed 1.4 wt%, most preferably does not exceed 1.2 wt% of the total fat content. LCPUFA as used in the present invention refers to polyunsaturated fatty acids with a 20 or 22 carbon chain. Preferably the present composition comprises at least 0.50 wt%, preferably at least 0.60 wt%, more preferably at least 0.70 wt% LC-PUFAs with 20 and 22 carbon atoms of the total fat content.

The EPA content preferably ranges between 0.25 and 0.35 wt% of the fatty acids, more preferably does not exceed 0.30 wt% of the fatty acids. The DHA content preferably ranges between 0.35 and 0.55 wt%, more preferably does not exceed 0.50 wt% of the fatty acids.

It is preferred that at least 80 wt%, more preferably at least 85 wt%, most preferably 85 – 100 wt% of the LCPUFAs with 20 and 22 carbon atoms is provided by the combination of EPA and DHA.

However, while the art promotes the use of significant amounts of ARA in infant formulae, it was found by the present inventors that excellent results are obtained when ARA levels are in fact low, preferably lower than 0.05 wt% of total fat. It is preferred that the composition comprises relatively low amounts, preferably less than 0.04 wt% of the total fat. The amount of ARA is preferably between 0 and 0.05 wt.%, more preferably between 0.01 and 0.05 wt.%.

If ARA is present, the weight ratio ARA:DHA preferably is below 0.2, more preferably below 0.15, most preferably below 0.10. If ARA is present, the weight ratio ARA:EPA is preferably less than 0.8, more preferably less than 0.5, most preferably less than 0.2. The weight ratio DHA:EPA is preferably in the range of 1:1 to 2:1, preferably about 3:2. It is noted that this is merely an approximate limit.

The DPA content preferably ranges between 0.01 and 0.20 wt% of the total fatty acids. Preferably, the present composition comprises 0.01- 0.15 gram docosapentaenoic acid (DPA, 22:5 n-3) per 100 g fatty acids.

It is preferred that the omega-6 LC-PUFA : omega-3 LC-PUFA weight ratio is between 1:1 and 7:1, more preferably between 2:1 and 6:1, most preferably between 3:1 and 5:1, most preferably less than 5:1, in particular less than 4.8:1.

The present composition preferably comprises between 5 and 75 wt% polyunsaturated fatty acids based on total fat, preferably between 10 and 50 wt%, most preferably between 10 and 25 wt%.

The LC-PUFAs with 20 and 22 carbon atoms 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 preferably comprises at least one of EPA and DHA, more preferably at least DHA, in triglyceride form. Preferably the present composition contains fish oil.

The present nutritional composition preferably also provides omega-9 (n-9) fatty acid (preferably oleic acid, 18:1), to provide sufficient nutrition. Preferably the present

composition provides at least 15 wt% n-9 fatty acid based on the weight of the total fatty acids, more preferably at least 25 wt%. The content of n-9 fatty acids is preferably below 80 wt%.

Oligosaccharides

The composition preferably comprises between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:

i) 1.4-2 gram galactooligosaccharides with a degree of polymerization of 2 – 7; and

ii) 0.1 - 0.5 gram fructopolysaccharides with degree of polymerization of 2 -150.

The term "fructopolysaccharides" comprises fructans and inulin, and hydrolyzates thereof. The preferred galactooligosaccharides are transgalactooligosaccharides. It is preferred that at least 95 wt%, preferably 95 – 100 wt% of the indigestible oligosaccharides is provided by galactooligosaccharides and fructopolysaccharides.

In a particularly preferred embodiment the present composition comprises transgalacto-oligosaccharide. Transgalacto-oligosaccharide can be defined as $[galactose]_n$-glucose and/or $[galactose]_n$-glucose-[galactose] wherein n is an integer from 1 up to and including 7. Preferably the present composition comprises $[galactose]_n$-glucose wherein n is an integer from 1 up to and including 6. This type of galactooligosaccharides is sometimes refered to as scGOS.

The term "fructo-polysaccharide" as used herein preferably refers to a non-digestible polysaccharide carbohydrate comprising a chain of at least 2 β-linked fructose units, with a DP of 2 to 250, preferably 7 to 100, more preferably 20 to 60. Preferably inulin is used. Inulin is available under the tradename "Raftilin HP®", (Orafti). The average DP of the present fructopolysaccharide is preferably at least 7, more preferably at least 10, preferably below 100, most preferably between 10 and 30, most preferably between 20 and 23. Fructopolysaccharide with an average DP between 10 and 30 is sometimes refered to as lcFOS. The fructopolysaccharide used preferably has the (majority of) fructose units linked with a β(2→1) linkage. Other terms for fructopolysaccharides include inulin, fructooligosaccharide, polyfructose, fructans and oligofructose. The

present composition preferably comprises fructopoly/oligosaccharides with a DP of 2 to 100.

Formula

The composition is preferably administered orally.

The present composition is preferably includes protein, carbohydrate and fat. It is preferably administered in liquid form. The term "liquid food" as used in the present invention includes dry food (e.g. powders) which are accompanied with instructions as to admix said dry food mixture with a suitable liquid (e.g. water).

The present composition is preferably provided as a packaged powder or packaged ready-to-feed formula. To prevent spoilage of the product, packaging size of ready-to-feed formula preferably does not exceed one serving, e.g. preferably does not exceed 1500 ml; and packaging size of the present composition in powder form preferably does not exceed 250 servings. Suitable packaging sizes for the powder are 2000 grams or less, preferably per 1000 grams or less.

Because lactose is an important carbohydrate source for young children, the present composition preferably comprises at least 35 wt% lactose based on weight of total digestible carbohydrate, more preferably at least 50 wt%, most preferably at least 75 wt%. Preferably, the composition comprises at least 1 g lactose/100 ml, more preferably at least 2 g/100ml, even more preferably at least 5 g per 100 ml. The present composition preferably comprises 4 g to 18 g, more preferably 4 to 14 g digestible carbohydrates per 100 ml composition.

Preferably, the composition comprises 4 to 20 en% protein, 20 to 50 en% fat, and 25 to 85 en% carbohydrates. More preferably, the composition comprises 8 to 10 en% protein, 35 to 45 en% fat, and 45 to 55 en% carbohydrates. "En%" is short for energy percentage and represents the relative amount each constituent contributes to the total caloric value of the preparation. The caloric value is provided by digestible carbohydrates, protein and fat. The protein may comprise a member selected form the group consisting of hydrolyzed milk protein, vegetable protein and/or amino acids.

In a preferred embodiment, the composition comprises vitamin D. Vitamin D is a group of fat-soluble secosteroids. There are two major physiologically relevant forms which are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). These are known collectively as calciferol. In the context of the invention, the term 'vitamin D' refers to all forms of vitamin D, either D1, D2, D3, or D4, in particular D2 and D3, or any mixture thereof. Excellent results are obtained with inclusion of vitamin D for immunity and infection, Vitamin D may be provided in an active ($1,25(OH)_2D$) or unactive (Vit D3 or D2) form.

The packaged products preferably provided with labels that explicitly or implicitly direct the consumer towards the use of said product in accordance with one or more of the above or below purposes, are encompassed by the present invention. Such labels may for example make reference to the present method by including wording like "reduced infection", "reduced infectious episodes", protects your child", "defense against bacteria and viruses", or similar wording, in accordance with the findings of the clinical study.

The present composition is preferably prepared by admixing a powdered composition comprising with water. The present invention thus also relates to a packaged power composition wherein said package is provided with instruction to admix the powder with a suitable amount of liquid.

In one preferred embodiment, the present composition is administered to a young child, wherein the above-mentioned oligosaccharides are administered in a dosage of 0.8 – 1.6 g/100 ml, preferably 1.0 – 1.4 g/100 ml, and wherein said n-3 LCPUFAs are administered in a dosage of 15 – 25 mg/100 ml, preferably 18 – 22 mg/100 ml.

Preferably the present composition is administered in liquid form to a young child in a daily amount of 250 – 750 ml, more preferably 400 – 750 ml per day, more preferably 400 – 600 ml per day, optimally about 500 ml per day. It is preferred that the daily dosage of the indigestible oligosaccharides (preferably GOS and fructopolysaccharides) is at least 3.5 gram and the daily dosage of n-3 LCPUFAs is at least 55 mg. It is however preferred that the oligosaccharides and the n-3 LCPUFAs are administered in a

daily dosage of about 5.0 – 7.0 g and 80 – 110 mg, respectively. The recommended daily amounts are about 6.0 and 100 mg for the oligosaccharides and the n-3 LCPUFAs, respectively. It is noted that these recommended values are merely approximate limits. In this paragraph, "the oligosaccharides" is to be understood as the combination of (i) short-chain galactooligosaccharides and (ii) long-chain fructopolysaccharides here above. The term "n-3 LCPUFAs" in this paragraph refers to the combination of DHA and EPA.

According to one embodiment, vitamin D is administered in an amount of 200 – 800 μg per daily dosage, preferably 300 – 700 μg, more preferably 400 – 600 μg per daily dosage. According to one embodiment, vitamin D is used in an amount of 40 – 160 μg per 100 ml, preferably 60 – 140 μg, more preferably 80 – 120 μg per 100 ml. The above numbers can be converted into IU if deemed appropriate.

Preferably the present composition is administered to the young child at least twice per week, more preferably at least 5 times per week, more preferably daily . Preferably the composition is administered for at least 10 consecutive weeks, preferably at least 26 consecutive weeks, more preferably at least 50 consecutive weeks.

Infections

The present invention relates to the use of the present composition in young children with the age between 10 and 48 months, preferably between 10 and 36 months, more preferably with the age between 11 and 40 months, more preferably from 1 year to 3 years. Preferably the young children are healthy children, preferably young children not diagnosed with an illness or disease.

The present invention preferably relates to intestinal and/or respiratory tract infections. Both the respiratory and intestinal tract are common sites for infection by pathogens. The present composition is preferably administered to young children attending daycare centers. These children are exposed to a plurality of microorganisms that can cause infections.

The present invention also provides for a packaged liquid or powder composition providing per 100 ml liquid composition or 100 ml in water reconstituted powder composition:

a. 15 – 25 mg long chain polyunsaturated fatty acids (LC-PUFAs) with 20 and 22 carbon atoms, wherein the amount of arachidonic acid (ARA) is less than 0.06 gram per 100 gram fatty acids; and comprising:
   (i) 0.3-0.6 gram docosahexaenoic acid (DHA, n-3) per 100 g fatty acids; and
   (ii) 0.2-0.4 gram eicosapentaenoic acid (EPA, n-3) per 100 g fatty acids; and
b. 1 – 1.5 gram indigestible oligosaccharides per 100 ml, and between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:
   (i) 1.4-2 gram per 100 kcal galactooligosaccharides with a degree of polymerization of 2 – 7; and
   (ii) 0.1 - 0.5 gram per 100 kcal fructopolysaccharides with degree of polymerization of 2 -150, and an average degree of polymerization between 10 and 30.

The composition is preferably used in the abovementioned method or use.

The composition preferably comprises 4 to 20 en% protein, 20 to 50 en% fat, and 25 to 85 en% carbohydrates. More preferably, the composition comprises 8 to 10 en% protein, 35 to 45 en% fat, and 45 to 55 en% carbohydrates.

In one embodiment, the packaged liquid or powder composition further comprises vitamin D, preferably in the forms and amounts indicated above.

EXAMPLE – clinical study

The study objective was to investigate the effect of the composition of the invention on the occurrence of infections in children attending daycare centers, age 1 – 3 years.
The study design is shown in Figure 1, the statistics given in Table 1.
The compositions of the control and the ‘ invention diet’ are listed in Table 2 (Table 2A showing the fatty acid compositions). The invention diet had a total saturated fatty acids content of 25.2 % (of all fatty acids); an omega-6:omega-3 weight ratio of 4.1:1; and a

LA:ALA weight ratio of 5.4:1. The numbers for the control diet were 24.9 %, 5.5:1 and 5.4:1, respectively.

Table 1. Number of participants in study

screened	907
Randomized	768
Reference group	37
SF at V2	103
Drop out after V2	73
completed	731

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Table 2: Ingredients [per 100 kg powder]

INGREDIENTS	**CONTROL**	**Invention diet**
Demineralized whey [kg]	21.0	19.4
Vegetable oils [kg]	21.2	19.1
Skimmed milk [kg]	17.7	16.3
Maltodextrin [kg]	17.3	13.5
Dietary fibers [kg]:	-	12.7
- galactooligosaccharides [kg]	-	11.9
- fructopolysaccharides [kg]	-	0.798
Lactose [kg]	16.6	12.6
Whey protein concentrate [kg]	3.97	3.58
tricalcium phosphate [kg]	0.460	0.398
Fish oil [kg]	-	0.384
Calcium carbonate [kg]	0.366	0.356
Tri potassium citrate [kg]	0.288	0.257
Tri sodium citrate [kg]	0.125	0.140
L-ascorbic acid [g]	95.1	87.4
Magnesium chloride[g]	79.7	66.8
Soy lecithin[g]	37.8	59.5
Taurine[g]	36.7	34.1
Choline chloride[g]	34.2	30.1

vanillin[g]	32.5	30.0
Sodium L-ascorbate[g]	32.5	29.9
Ferrous sulphate[g]	25.9	23.8
Potassium chloride[g]	21.5	23.0
Zinc sulphate[g]	15.4	13.9
DL-alpha tocopheryl acetate[g]	3.89	3.62
Nicotinamide[g]	3.13	2.87
Folic acid[g]	1.32	1.21
Cholecalciferol[g]	1.30	1.19
Calcium D-pantothenate[g]	1.24	1.08
Cupric sulphate[g]	1.16	1.07
Retinyl palmitate[g]	0.959	0.879
DL-alpha tocopherol[g]	0.913	0.836
D-biotin[g]	0.694	0.638
Retinyl acetate[g]	0.661	0.627
Thiamin hydrochloride[g]	0.436	0.402
Cyanocobalamin[g]	0.251	0.325
Pyridoxine hydrochloride[g]	0.246	0.245
Riboflavin[g]	0.206	0.226
Potassium iodide[mg]	87.4	67.0
Manganese sulphate[mg]	75.6	54.6
Phytomenadione[mg]	29.9	27.4
Sodium selenite[mg]	21.9	20.3

Table 2A – Fatty acid composition*

	CONTROL		**Invention diet**	
	Per 100 g fatty acids	Per 100 g powder	Per 100 g fatty acids	Per 100 g powder
C16:0 palmitic acid	19.2	3.96	19.2	3.62
C18:0 stearic acid	3.48	0.72	3.50	0.66
C18:1 oleic acid	57.3	11.8	56.3	10.7
C18:2 linoleic acid	14.2	2.93	14.0	2.65

C18:3 alpha-linolenic acid	2.64	0.542	2.60	0.492
C20:0 aracidic acid	0.42	0.09	0.42	0.08
C20:1 eicosaenoic acid	0.55	0.11	0.268	0.051
C20:4 arachidonic acid	-	-	0.034	0.006
C20:5 eicosapentaenoic acid	-	-	0.268	0.051
C22:0 behenic acid	0.44	0.09	0.44	0.08
C22:1 erucic acid	0.11	0.02	0.11	0.02
C22:5 docosapentaenoic acid	-	-	0.06	0.01
C22:6 doxosahexaenoic acid	-	-	0.402	0.076

*The list of fatty acids is not exhaustive. Listed are those present in significant amounts and considered relevant for the purpose of the study.

In a randomized, double-blind, controlled, parallel, multi-country intervention trial, 767 healthy children, aged 11-29 months, received the 'invention diet' with scGOS/lcFOS/LCPUFA, or 'control diet' (without scGOS/lcFOS/LCPUFA) for 52 weeks.

Aimed daily intake of at least 6.0g of scGOS/lcFOS and 100 mg of n-3 LCPUFA (DHA and EPA) in 500 ml. The composition included 1.2g/100 ml of scGOS/lcFOS and 19.2 mg/100 ml of n-3 LCPUFA (DHA and EPA).

Parents completed a daily diary on occurring illness symptoms (not distinguishing between upper respiratory tract infections and gastrointestinal infections).
A Zero-inflated Negative – Binomial regression Model was used that combines two separate parts: a binomial part (a subject would get an infection: yes/no) and a negative-binomial part fitting the counts for infections for the subjects.

As a result, children in the 'invention diet' group compared with the control group had a decreased risk of having at least one infection (299/388 (77%) vs. 313/379 (83%), respectively, RR = 0.93, 95% CI 0.87-1; chi-square p=0.057; logistic regression p=0.0259).

In words, the results show a trend toward a significant effect on number of infectious episodes ($p = 0.0743$). This trend is driven by a significant increased chance of having no infectious episode, as shown in Figure 2, in terms of the percentage of young children that were not reported to have suffered from infectious episodes ($p < 0.05$).

CLAIMS

1. A composition for use in reducing the occurrence of infection in young children, reducing the number of infectious episodes in young children and/or the treatment and/or prevention of infections in young children, said composition comprising:
   a) long chain polyunsaturated fatty acids (LC-PUFAs) with 20 and 22 carbon atoms, wherein the amount of arachidonic acid (ARA) is less than 0.06 gram per 100 gram fatty acid; and comprising:
      (i) 0.3-0.6 gram docosahexaenoic acid (DHA, n-3) per 100 g fatty acids; and
      (ii) 0.2-0.4 gram eicosapentaenoic acid (EPA, n-3) per 100 g fatty acids; and
   b) between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:
      (i) 1.4-2 gram galactooligosaccharides with a degree of polymerization of 2 – 7; and
      (ii) 0.1 - 0.5 gram fructopolysaccharides with degree of polymerization of 2 -150.

2. The composition for use according to claim 1, wherein at least 80 wt% of said LCPUFAs are provided by the combination of EPA and DHA.

3. The composition for use according to any one of the preceding claims, comprising 0.01- 0.2 gram docosapentaenoic acid (DPA, n-3) per 100 g fatty acids.

4. The composition for use according to any one of the preceding claims wherein at least 95 wt% of the indigestible oligosaccharides are provided by galactooligosaccharides and fructopolysaccharides.

5. The composition for use according to any one of the preceding claims, comprising 8-10 energy % protein, 45-55 energy % carbohydrates and 35-45 en% fat; and 0.5-0.75 kcal per 100 ml.

6. The composition for use according to any one of the preceding claims, wherein said infections comprise respiratory tract infections and intestinal infections. The composition according to any one of the preceding claims, having a weight ratio of ARA:DHA below 0.2.

7. The composition for use according to any one of the preceding claims, having a weight ratio of ARA:EPA below 0.8.

8. The composition for use according to any one of the preceding claims, having an omega-6 LC-PUFA : omega-3 LC-PUFA weight ratio between 1:1 and 7:1.

9. The composition for use according to any one of the preceding claims, having a weight ratio of DHA:EPA in the range of 1:1 to 2:1.

10. The composition for use according to any one of the preceding claims, further comprising vitamin D, preferably in a daily dosage of 200 – 800 μg.

11. Use of a composition in the manufacture of a product for reducing the occurrence of infection in young children, reducing the number of infectious episodes in young children, and/or the treatment and/or prevention of infections in young children, said composition comprising:
    a) long chain polyunsaturated fatty acids (LC-PUFAs) with 20 and 22 carbon atoms, wherein the amount of arachidonic acid (ARA) is less than 0.06 gram per 100 gram fatty acid; and comprising:
        (i) 0.3-0.6 gram docosahexaenoic acid (DHA, n-3) per 100 g fatty acids; and
        (ii) 0.2-0.4 gram eicosapentaenoic acid (EPA, n-3) per 100 g fatty acids;
    b) between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:
        (i) 1.4-2 gram galactooligosaccharides with a degree of polymerization of 2 – 7; and
        (ii) 0.1 - 0.5 gram fructopolysaccharides with degree of polymerization of 2 -150.

12. Use according to claim 11, wherein said infections comprise respiratory tract infections and intestinal infections.

13. Use according to claim 12 , wherein at least 80 wt% of said LCPUFAs are provided by the combination of EPA and DHA.

14. Use according to any one of claims 11 - 13, wherein at least 95 wt% of the indigestible oligosaccharides are provided by galactooligosaccharides and fructopolysaccharides.

15. Use according to any one of claims 11 - 14, said composition comprising 8-10 energy % protein, 45-55 energy % carbohydrates and 35-45 en% fat; and 0.5-0.75 kcal per 100 ml.

16. Use according to any one of claims 11 - 15, wherein said infections comprise respiratory tract infections and intestinal infections.

17. Use according to any one of claims 11 - 16, said composition having a weight ratio of ARA:DHA below 0.2.

18. Use according to any one of claims 11 - 17, said composition having a weight ratio of ARA:EPA below 0.8.

19. Use according to any one of claims 11 - 18, said composition having an omega-6 LC-PUFA : omega-3 LC-PUFA weight ratio between 1:1 and 7:1.

20. Use according to any one of claims 11 - 19, said composition having a weight ratio of DHA:EPA in the range of 1:1 to 2:1.

21. Use according to any one of claims 11 - 20, said composition further comprising vitamin D, preferably in a daily dosage of 200 – 800 μg.

22. A packaged liquid or powder composition providing per 100 ml liquid composition or 100 ml in water reconstituted powder composition:
    a. 15 – 25 mg long chain polyunsaturated fatty acids (LC-PUFAs) with 20 and 22 carbon atoms, wherein the amount of arachidonic acid (ARA) is less than 0.06 gram per 100 gram fatty acid; and comprising:
        (i) 0.3-0.6 gram docosahexaenoic acid (DHA, n-3) per 100 g fatty acids; and
        (ii) 0.2-0.4 gram eicosapentaenoic acid (EPA, n-3) per 100 g fatty acids; and
    b. 1 – 1.5 gram indigestible oligosaccharides per 100 ml, and between 1.5 and 2.5 gram indigestible oligosaccharides per 100 kcal, comprising:
        (i) 1.4-2 gram per 100 kcal galactooligosaccharides with a degree of polymerization of 2 – 7; and
        (ii) 0.1 - 0.5 gram per 100 kcal fructopolysaccharides with degree of polymerization of 2 -150, and an average degree of polymerization between 10 and 30;
    c. 8 to 10 en% protein, 35 to 45 en% fat, and 45 to 55 en% carbohydrates.

Fig. 1

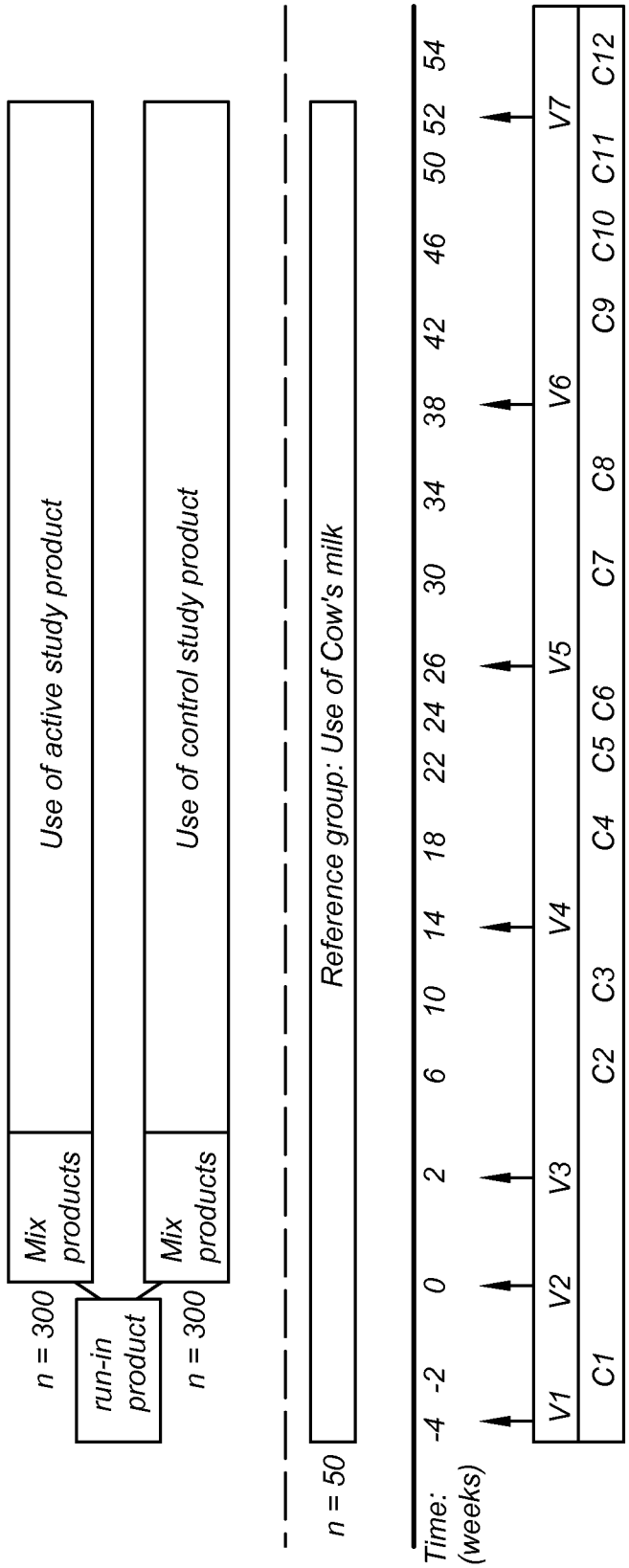
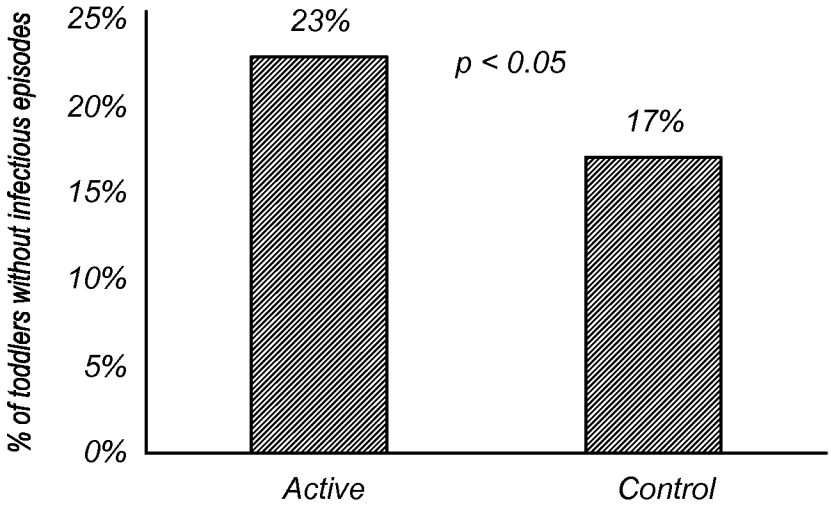

n = 300
Mix products
run-in product
n = 300
Mix products
Use of active study product
Use of control study product
n = 50
Reference group: Use of Cow's milk
Time: (weeks)
-4 -2 0 2 6 10 14 18 22 24 26 30 34 38 42 46 50 52 54
V1 V2 V3 V4 V5 V6 V7
C1 C2 C3 C4 C5 C6 C7 C8 C9 C10 C11 C12

Fig. 2


% of toddlers without infectious episodes
25%
20%
15%
10%
5%
0%
23%
17%
p < 0.05
Active
Control

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2011/050449

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L1/29 A23L1/30 A23L1/308 A61P11/00 A61K31/20
A61K31/202 A61K31/702 A61K31/733
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A23L A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 2012	28/03/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Tallgren, Antti

INTERNATIONAL SEARCH REPORT

International application No
PCT/NL2011/050449

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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