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(54) Title: GENDER SPECIFIC SYNTHETIC NUTRITIONAL COMPOSITIONS AND, NUTRITIONAL SYSTEMS COMPRISING THEM

(57) Abstract: Gender specific synthetic nutritional compositions for female or male infants of 1 to 2 months of age wherein, the concentration of arginine is adapted based on that found in HM produced for an infant of the same gender and age, and nutritional systems comprising them.

Title: Gender specific synthetic nutritional compositions and, nutritional systems comprising them.

Technical field: The invention relates to gender specific synthetic nutritional compositions, to nutritional systems comprising them and, to their use to provide optimised nutrition and/or one or more health benefit to an infant.

Background of the invention

Even though breastfeeding is optimal for infants, the existence of certain conditions may mean that it is contraindicated (AAP, 2012; Lawrence, 2013). In such cases, where the sole source of nutrition is not available to the infant, alternative strategies to feed them have to be devised. Feeding infants with Synthetic nutritional compositions e.g. Infant formula is one such strategy.

The compositions of the aforementioned synthetic nutritional compositions are modeled on those of human milk. However, the composition of HM is extremely dynamic and these dynamic changes remain largely unexplored and uncharacterized. Whilst it is known that components and/or their quantities may vary depending on a variety of factors including the stage of lactation, circadian rhythms and even gender, it is not known which of the numerous components vary and if so how they vary e.g. by stage of lactation and/or gender.

Surprisingly it has now been identified that 1 month to 2 months postpartum, there can be a difference in the concentration range of arginine found in HM produced by mothers to girls in comparison to mothers to boys. This finding stems from a cross-sectional study of HM wherein, HM samples from mothers to either boys or girls were collected at various stages postpartum and analysed. Further, it was also surprisingly found that 1 month to 2 months postpartum, the

mean concentration of arginine in HM produced by mothers to boys was lower than that produced for mothers to girls.

Because these gender difference in the concentration of arginine have never been previously identified, they are not reflected in the compositions of synthetic nutritional compositions available today.

Arginine is an amino acid. Optimum intake of amino acids helps to ensure optimum growth and development in infants.

Optimum growth and development may be immediate and/or long term. Long term may only be evident in months or years e.g. 6 months, 9 months, 12 months, 5 years, 10 years, or 20 years.

Accordingly, there remains a need for gender specific synthetic nutritional compositions, and nutritional systems comprising them, having compositions within which the identified gender differences, with respect to the concentration of arginine, found in HM 1 month to 2 months postpartum, are more accurately reflected and thereby optimised.

Summary of the invention

The invention is set out in the claims. The inventors have found that the concentration range of arginine in HM can vary 1 month to 2 months postpartum depending on the gender of the mother's infant. In light of this finding the inventors have developed gender specific nutritional compositions, and nutritional systems comprising them, that reflect the identified gender

differences. Prior to aforementioned findings the skilled person has no incentive to develop such gender specific synthetic nutritional compositions or to include them in nutritional systems.

The concentration of arginine in the gender specific synthetic nutritional compositions of the invention, and the nutritional systems comprising them, more accurately reflect its concentration in HM produced for infants of the same gender and age. In light of this and, because HM is considered optimal with respect to infant nutrition, they can provide an optimized amount of arginine to an infant, in particular an infant of 1 month to 2 months of age.

The gender specific synthetic nutritional compositions can be prepared from a gender neutral synthetic nutritional composition by measuring out an appropriate amount of said gender neutral synthetic nutritional composition and mixing it with an additive and/or diluent.

Since optimized arginine intake helps to ensure the optimum growth and development of an infant, the gender specific synthetic nutritional compositions, and nutritional systems of the invention, can also be used to treat, prevent or mitigate sub optimal growth of an infant e.g. obesity of an infant.

Optionally the gender specific synthetic nutritional composition is selected from the group consisting of: infant formula, and a composition for infants that is intended to be added or diluted to human milk e.g. HM fortifier .

In addition to that set out above, the inventors have also found that the mean concentration of arginine in HM does not vary by gender before 1 month or after 2 months postpartum. In light of this, in addition to comprising the gender specific synthetic nutritional compositions of the invention, the nutritional systems disclosed herein may optionally also comprise synthetic nutritional compositions for infants less than 1 month of age, or more than 2 months of age

wherein, the concentration of arginine does not differ by gender for infants of the same age. Accordingly, the nutritional systems of the invention may also provide optimized nutrition and/or one or more health benefits for an infant, in particular an infant up to 12 months of age, up to 9 months of age, up to 8 months of age, up to 6 months of age, up to 5 months of age, up to 3 months of age, up to 1 months of age.

Drawings

FIG.1 is a graphical representation of the identified difference in the mean concentration of arginine in HM by gender at up to 2 weeks (5-11 days), 2 weeks to 1 month (12-30 days), 1 to 2 months (31 to 60 days) , 2 to 4 months (61 to 120 days)and, 2 to 8 months (121 to 240 days) postpartum.

Detailed Description

As stated herein, the inventors performed a cross sectional study evaluating the nutrient composition of HM collected from mothers at various stages of lactation (up to 2 weeks (5-11 days), 2 weeks to 1 month (12-30 days), 1 to 2 months (31 to 60 days), 2 to 4 months (61 to 120 days) and, 4 to 8 months (121 to 240 days) postpartum). The study indicated that there can be different min and max ranges for the concentration of arginine by gender. Surprisingly, the results of this study also indicated that that 1 month to 2 months postpartum, there is a difference in the mean concentration of arginine in HM depending on the gender of the mother's infant. Further details of the study, analysis techniques and results are given in example 1.

Based on the findings of the study, the inventors have designed gender specific synthetic nutritional compositions for infants 1 month to 2 months of age wherein, the concentration of arginine is adapted based on that found in HM produced for an infant of the same gender and age.

The term "gender specific synthetic nutritional composition" as used herein refers to any synthetic nutritional composition, intended to be consumed by an infant that is specifically adapted to the nutritional needs of either a female or male enfant.

Non limiting examples of gender specific synthetic nutritional compositions for infants from birth to 4 months include; infant formulae, and a composition for infants that is intended to be added or diluted with HM e.g. HM fortifier. Non limiting examples of gender specific synthetic nutritional compositions for infants from 4 months to 12 months include infant formulae, a composition for infants that is intended to be added or diluted with HM e.g. HM fortifier, or food stuffs intended for consumption by infants either alone or in combination with HM e.g. complementary foods.

The term "infant" as used herein refers to a human infant of 12 months of age or less.

In a first aspect of the invention there is provided a gender specific synthetic nutritional composition for an infant 1 month to 2 months of age wherein, the concentration of arginine is adapted based on that found in HM produced for an infant of the same gender and age.

The concentration of arginine is a measure of the total concentration of both the D and L forms of said amino acids, whether free or bound i.e. protein bound.

The gender specific synthetic nutritional composition can be a male specific synthetic nutritional composition or a female specific synthetic nutritional composition for an infant of 1 month to 2 months of age.

In an embodiment the gender specific synthetic nutritional composition is a female specific synthetic nutritional composition for an infant of 1 month to 2 months of age and comprises arginine in a concentration of 49.1 to 142.3, 78.22 to 142.3, 49.1 to 121.38, 62.16 to 101.64, or 81.9, mg/100g.

In an embodiment the gender specific synthetic nutritional composition is a male specific synthetic nutritional composition for an infant of 1 month to 2 months of age, and comprises arginine in a concentration of 47.4 to 142.3, 47.4 to 106.46, 47.4 to 78, 57.91 to 84.95, or 74.54 mg/100g.

The concentration of arginine can be measured by methods well known in the art. In particular its concentration can be measured by an amino acid analyzer (using post-column derivatisation with ninhydrin) or by a pre-column derivatisation method (i.e. using PITC or OPA/FMOC chemistry as described in Blankenship D.T. et al. (1989) *Analytical Biochemistry* 178: 227) followed by HPLC separation and quantification.

Any source of Arginine known to be employed in the types of synthetic nutritional compositions disclosed herein may be comprised within in the gender specific synthetic nutritional

compositions of the invention, in particular pure synthetic arginine obtained through synthesis or fermentation, or liberated from any food-grade protein source such as animal or plant proteins through hydrolysis.

The arginine may be intact, hydrolysed, partially hydrolysed, or any combination thereof.

The gender specific synthetic nutritional compositions of the invention can also comprise any other ingredients or excipients known to be employed in synthetic nutritional compositions.

Non limiting examples of such ingredients include: other amino acids, proteins, carbohydrates, oligosaccharides, lipids, prebiotics or probiotics, essential fatty acids, nucleotides, nucleosides, vitamins, minerals and other micronutrients.

Non limiting examples of other amino acids include, alanine, histidine, isoleucine, proline, valine, cysteine, glutamine, glutamic acid, glycine, serine, leucine, threonine, tyrosine, lysine, methionine, phenylalanine, tryptophane, asparagine, aspartic acid, and combinations thereof.

Non limiting examples of proteins include, caseins, alpha-lactalbumin, lactoferrin, serum albumin, whey, soy protein, rice protein, corn protein, oat protein, barley protein, wheat protein, rye protein, pea protein, egg protein, sunflower seed protein, potato protein, fish protein, meat protein, immunoglobins and, combinations thereof.

Non limiting examples of carbohydrates include lactose, saccharose, maltodexirin, starch, and mixtures thereof

Non limiting examples of lipids include: palm olein, high oleic sunflower oil, high oleic safflower oil, canola oil, fish oil, coconut oil, bovine milk fat, or mixtures thereof.

Non limiting examples of essential fatty acids include: linoleic acid (LA), α-linolenic acid (ALA) and polyunsaturated fatty acids (PUFAs). The nutritional compositions of the invention may further contain gangliosides monosialoganglioside-3 (GM3) and disialogangliosides 3 (GD3), phospholipids such as sphingomyelin, phospholipids phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, and combinations of the foregoing.

None limiting examples of prebiotics include: oligosaccharides optionally containing fructose, galactose, mannose; dietary fibers, in particular soluble fibers, soy fibers; inulin; or mixtures thereof. Preferred prebiotics are fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), isomalto-oligosaccharides (IMO), xylo-oligosaccharides (XOS), arabino-xylo oligosaccharides (AXOS), mannan-oligosaccharides (MOS), oligosaccharides of soy, glycosylsucrose (GS), lactosucrose (LS), lactulose (LA), palatinose-oligosaccharides (PAO), malto-oligosaccharides, gums and/or hydrolysates thereof, pectins and/or hydrolysates thereof, and combinations of the foregoing.

Further examples of oligosaccharide are described in Wrodnigg, T. M.; Stutz, A.E. (1999) Angew. Chem. Int. Ed. 38:827-828 and in WO 2012/069416 which is incorporated herein by reference.

Non limiting examples of probiotics include: *Bifidobacterium*, *Lactobacillus*, *Lactococcus*, *Enterococcus*, *Streptococcus*, *Kluyveromyces*, *Saccharoymces*, *Candida,* in particular selected

from the group consisting of *Bifidobacterium longum*, *Bifidobacterium lactis*, *Bifidobacterium animalis*, *Bifidobacterium breve*, *Bifidobacterium infantis*, *Bifidobacterium adolescentis*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus paracasei*, *Lactobacillus salivarius*, *Lactobacillus lactis, Lactobacillus rhamnosus*, *Lactobacillus johnsonii*, *Lactobacillus plantarum*, *Lactobacillus salivarius, Lactococcus lactis*, *Enterococcus faecium*, *Saccharomyces cerevisiae*, *Saccharomyces boulardii* or mixtures thereof, preferably selected from the group consisting of *Bifidobacterium longum* NCC3001 (ATCC BAA-999), *Bifidobacterium longum* NCC2705 (CNCM I-2618), *Bifidobacterium longum* NCC490 (CNCM I-2170), *Bifidobacterium lactis* NCC2818 (CNCM I-3446), *Bifidobacterium breve* strain A, *Lactobacillus paracasei* NCC2461 (CNCM I-2116), *Lactobacillus johnsonii* NCC533 (CNCM I-1225), *Lactobacillus rhamnosus GG* (ATCC53103), *Lactobacillus rhamnosus* NCC4007 (CGMCC 1.3724), *Enterococcus faecium SF 68* (NCC2768; NCIMB10415), and mixtures thereof.

Non limiting examples of Nucleotides include: cytidine monophosphate (CMP), uridine monophosphate (UMP), adenosine monophosphate (AMP), guanosine monophosphate (GMP) or any mixtures thereof.

Non limiting examples of vitamins and minerals include: vitamin A, vitamin B1, vitamin B2, vitamin B6, vitamin Bi2, vitamin E. vitamin K. vitamin C, vitamin D, folic acid, inositol, niacin, biotin, pantothenic acid, choline, calcium, phosphorous, iodine, iron, magnesium, copper, zinc, manganese, chloride, potassium, sodium, selenium, chromium, molybdenum, taurine, and L-carnitine, and mixtures thereof. Minerals are usually added in salt form.

Other suitable and desirable ingredients of synthetic nutritional compositions, that may be employed in the gender specific nutritional compositions of the invention, are described in guidelines issued by the Codex Alimentarius with respect to the type of synthetic nutritional composition in question e.g. Infant formula, HM fortifier, follow on formula, and food stuffs intended for consumption by infants e.g. complementary foods.

The gender specific compositions of the invention may be prepared by methods well known in the art for preparing that type of synthetic nutritional composition e.g. infant formulae, follow on formulae, a composition for infants that is intended to be added or diluted with HM e.g. HM fortifier, or, food stuffs intended for consumption by infants either alone or in combination with HM e.g. complementary foods.

An exemplary method for preparing a gender specific powdered infant formula is as follows. Amino acids (optionally including arginine), and/or protein source (optionally including protein comprising bound arginine), carbohydrate source, and fat source may be blended together in appropriate proportions. Emulsifiers maybe included in the blend. Vitamins and minerals may be added at this point but are usually added later to avoid thermal degradation. Any lipophilic vitamins, emulsifiers and the like may be dissolved into the fat source prior to blending. Water, preferably water which has been subjected to reverse osmosis, may then be mixed in to form a liquid mixture.

The liquid mixture may then be thermally treated to reduce bacterial loads. For example, the liquid mixture may be rapidly heated to a temperature in the range of about 80^0C to about 110^0C for about 5 seconds to about 5 minutes. This may be carried out by steam injection or by

heat exchanger; for example a plate heat exchanger.

The liquid mixture may then be cooled to about 60^0C to about 85^0C; for example by flash cooling. The liquid mixture may then be homogenised; for example in two stages at about 7 MPa to about 40 MPa in the first stage and about 2 MPa to about 14 MPa in the second stage. The homogenised mixture may then be further cooled to add any heat sensitive components such as vitamins and minerals. The pH and solids concentration in the homogenised mixture is conveniently standardised at this point.

The homogenised mixture can be transferred to a suitable drying apparatus such as a spray drier or freeze drier and converted to powder. The powder should have a moisture concentration of less than about 3% by weight.

If it is desired probiotic(s) can be added, they may be cultured according to any suitable method and prepared for addition to the infant formula by freeze-drying or spray-drying for example. Alternatively, bacterial preparations can be bought from specialist suppliers such as Christian Hansen and Morinaga already prepared in a suitable form for addition to food products such as infant formula. Such bacterial preparations may be added to the gender specific powdered infant formula by dry mixing.

The gender specific compositions of the invention may also be prepared from a gender neutral synthetic nutritional composition in a method comprising; measuring out an appropriate amount of said gender neutral synthetic nutritional composition and mixing it with an additive and/or diluent e.g. water so as to arrive at a gender specific nutritional composition in accordance with the invention.

The additive may be a gender specific additive comprising arginine in a particular concentration so that when mixed with the gender neutral synthetic nutritional composition, and optionally a diluent, the resulting mixture is a gender specific synthetic nutritional composition of the invention.

The gender neutral synthetic nutritional composition can be prepared by methods well known in the art. For example, as laid out above for infant formula.

One or more of the gender specific synthetic nutritional compositions of the invention can be included in a nutritional system.

The term "nutritional system" as used herein refers to a collection of more than one synthetic nutritional composition advertised or sold as part of the same product range e.g. a collection of infant formulas sold under the same brand and adapted to the nutritional needs of infants of differing genders and/or ages. The synthetic nutritional compositions making up the nutritional system may be packaged individually e.g. in capsules or boxes. Said packages can be sold individually, grouped together e.g. wrapped by plastic film or combined in a box or, in a combination of these two ways.

The nutritional system may comprise only gender specific synthetic nutritional compositions, or, it may comprise a mix of gender specific and gender neutral synthetic nutritional compositions.

The term "gender neutral" as used herein is synonymous with unisex.

In a further aspect of the present invention there is provided a nutritional system comprising at least one of the gender specific synthetic nutritional compositions of the invention.

In an embodiment the nutritional system comprises a gender specific synthetic nutritional composition for a male infant of 1 month to 2 months of age, and, a gender specific synthetic nutritional composition for female infant of 1 month to 2 months of age.

In an embodiment the concentration of arginine in said female gender specific synthetic nutritional composition is higher than that of said male gender specific synthetic nutritional composition.

The concentration of arginine in the female gender synthetic nutritional compositions may be higher by any amount.

In an embodiment the ratio of the concentration of arginine between the female gender specific nutritional composition and male gender specific synthetic nutritional composition is 1:0.9 to 1:0.99, or 1:0.9 to 1:0.97.

In an embodiment the female gender specific synthetic nutritional composition contains 0.001 to 7.36, or 1.7 to 7.36, mg/100g more arginine than the male gender specific synthetic nutritional composition.

In addition to that disclosed hereinabove, the referenced study further indicated that up to 30 days and 61 days to 240 days postpartum there is no difference in the mean concentration of arginine in HM depending on the gender of the mother's infant.

In another embodiment the nutritional system further comprises gender specific synthetic nutritional compositions for infants up to 1 month of age and/or more than 2 months of age wherein, the concentration of arginine does not differ by gender for infants of the same age.

In another embodiment the nutritional system further comprises gender neutral specific synthetic nutritional compositions for infants up to 1 month of age and/or more than 2 months of age.

Non limiting examples of ages, or ranges thereof, less than 1 month of age, include: up to 2 weeks, Up to 1 month.

Non limiting examples of ages, or ranges thereof, more than 2 months of age, include: , 2-4mths, 3 months, 3-6mths, 4-6mths, 4-8mths 6-12mths, 7-12mths.

The nutritional system may further comprise nutritional compositions for children older than 12months.

A gender specific synthetic nutritional composition and/or nutrition system according to the invention is particularly suitable for use in a method of preparing single servings of infant formula using capsules, each capsule of which contains a unit dose of a synthetic nutritional composition in concentrated form, and which is equipped with opening means contained within the capsule to permit draining of the reconstituted synthetic nutritional composition directly from the capsule into a receiving vessel such as a baby bottle. Such a method is described in WO2006/077259.

The different synthetic nutritional compositions, including gender specific and gender neutral synthetic nutritional compositions, which may be comprised within a nutrition system, may be

packed into individual capsules and presented to the consumer in multipacks containing a sufficient number of capsules to meet the requirements of an infant of a particular age or range for one week for example. Suitable capsule constructions are disclosed in WO2003/059778.

The capsules can contain the synthetic nutritional compositions, (gender specific and gender neutral) in the form of powders or concentrated liquids in both cases for reconstitution by an appropriate amount of water. Both the composition and the quantity of infant formula in the capsules may vary according to the gender and/or age of the infant. If necessary, different sizes of capsules may be provided for the preparation of infant formulas for infants of different genders and/or ages.

The gender specific synthetic nutritional compositions, or nutritional systems comprising them, better reflect the differences in the concentration of arginine in HM found by gender at one or more stages of lactation. As stated herein, optimum arginine intake helps to ensure the optimum growth and development of an infant.

In another aspect of the present invention there is provided a gender specific synthetic nutritional composition and/or nutritional system as disclosed herein for use to treat, prevent or mitigate sub optimal growth of an infant e.g. obesity.

In another aspect of the present invention there is provided the use of a gender specific synthetic nutritional composition and/or nutritional system as disclosed herein for use in the manufacture of a medicament for use to treat, prevent or mitigate sub optimal growth and development e.g. obesity, of an infant.

A gender specific synthetic nutritional composition may provide an optimum amount of arginine, to an infant, in particular an infant of 1 month to 2 months of age.

The nutritional system may provide an optimum amount of arginine to an infant, in particular an infant up to 12 months of age, up to 9 months of age, up to 8 months of age, up to 6 months of age, up to 1 month of age, up to 2 weeks of age.

In another aspect of the present invention there is provided a method for providing an optimum amount of arginine to an infant, in particular an infant of 1 month of age to 2 months of age comprising:

a) Optionally preparing a gender specific synthetic nutritional composition according to the invention from a gender neutral synthetic nutritional composition;
b) Feeding a gender specific synthetic nutritional compositions according to the invention to an infant of 1 month to 2 months of age.

As stated herein. The gender specific synthetic nutritional compositions may be prepared from gender neutral synthetic nutritional compositions. Accordingly, in another aspect of the present invention there is provided a kit for providing an optimized amount of arginine to an infant, in particular an infant of 1 month to 2 month of age, the kit comprising:

a) A gender neutral synthetic nutritional composition
b) A label indicating dosage requirements for an infant so as to arrive at a gender specific nutritional composition in accordance with the invention.

The dosage requirements may be with respect to the quantity of the gender neutral synthetic nutritional employed and/or consumption frequency e.g. 4 times per day.

Subjects included in the survey referenced herein were recruited from 4 provinces across China. Accordingly, the gender specific synthetic nutritional compositions and/or nutritional systems disclosed herein can be particularly relevant for Chinese infants, and or infants born in populations having common genetic origins and/or ethnic origins and/or common dietary habits thereto e.g. Asian, Indian, and/or Mongoloid populations.

It should be appreciated that all features of the present invention disclosed herein can be freely combined and that variations and modifications may be made without departing from the scope of the invention as defined in the claims. Furthermore, where known equivalents exist to specific features, such equivalents are incorporated as if specifically referred to in this specification.

There now follows a series of non-limiting examples that serve to illustrate the invention.

Examples

Example 1

The concentration of arginine in HM samples collected from mothers to either male or female infants was analysed at various stages postpartum. The HM samples were collected as part of a cross sectional survey of HM. The study criteria is set out below:

Study population

• Number of subjects

Total 540 healthy subjects were enrolled, allowing a drop-out rate of 10 percent. They were comprised of:

– 480 Lactating mothers in 3 cities (Beijing, Suzhou and Guangzhou)

– 30 mothers per city for each of the 5 time points (5 to11 days, 2 weeks to 1 month, 1 to 2 months, 2 to 4 months and, 4 to 8 months)

Inclusion/Exclusion criteria

• Inclusion: Healthy Chinese lactating mothers without history of acute and chronic diseases; exclusively breast feeding mothers during 4 months after delivery were enrolled.

• Exclusion: Chinese lactating mothers having history of psychopathic tendencies and having no dietary memory.

The concentration of arginine in the HM samples collected as part of the above detailed study was analyzed using firstly acid hydrolysis in 6 M hydrochloric acid at 110°C for 22 hrs with phenol antioxidant in the absence of oxygen to liberate all protein-bound arginine, followed

secondly by high-sensitivity amino acid analysis using derivatisation with o-Phthalaldehyde (OPA) and 9-Fluorenylmethyl Chloroformate (FMOC), and fluorescence detection (Blankenship D.T. et al. (1989) *Analytical Biochemistry* 178: 227).

The results of the compositional analysis of the HM survey, with respect to the concentration of arginine are shown in table I.

Arginine concentration mg/100 g								
	Female				Male			
Stage	Min	Mean	SD	Max	Min	Mean	SD	Max
5 to 11 days	28	111.22	42.29	248.4	69.6	113.17	32.37	248.4
2 weeks to 1 month	50.1	90.52	20.12	140.1	58.7	96.18	26.76	214.1
1 to 2 months	49.1	81.9	19.74	142.3	47.4	74.54	15.96	142.3
2 to 4 months	31.8	66.56	94.8	94.8	26.9	64.36	15.02	107.2
4 to 8 months	37.6	65.63	99.2	99.2	46.4	67.53	14.05	103.5

Table I

The results of the compositional analysis were then subject to a statistical analysis employing the following statistical model:

Concentration = sex + timeframe + timeframe + sex : timeframe – city + ε

ε referring to the residual error and *sex:timeframe* referring to the interaction between these 2 variables.

Table II shows the estimates for gender differences per timeframe along with the corresponding Pvalues for arginine.

Timeframe	Variable	Estimate	lower	Upper	Pvalue
5 to 11 days	Arginine	-1.698725	-10.806659	7.40921	0.714183
2 weeks to 1 month	Arginine	-5.165925	-14.502830	4.17098	0.277532
1 to 2 months	Arginine	8.308003	-0.760405	17.37641	0.072466
2 to 4 months	Arginine	1.900203	-7.013910	10.81432	0.675522

4 to 8 months	Arginine	-0.737446	-9.797494	8.32260	0.873005

Table II

A P-value inferior to 0.1 for a particular timeframe suggests that there is a statistically significant difference in the arginine concentration in HM produced for males and females infants at that specific timeframe.

As can be seen from the results in table II, a statistically significant difference in the arginine concentration between HM produced for male and female infants was identified at 1 month to 2 months postpartum. No statistically significant difference was identified in the arginine concentration between HM produced for male and female infants up to 1 month of age and/or older than 61 days postpartum Viz. 2 to 4 months and 4 to 8 months.

months.

Example 2

Examples of gender specific infant formulas are given in table III

	1 month to 2 months of age	
	F	M
Ingredients	Per Litre	
Energy (kcal)	670	670
Protein (g)	9.1	9.1
Arginine (Free or protein bound) (g)	0.081	0.074
Fat (g)	35.7	35.7
Linoleic acid (g)	5.3	5.3
α-Linolenic acid (mg)	675	675
Lactose (g)	74.7	74.7
Prebiotic (100% GOS) (g)	4.3	4.3
Minerals (g)	2.5	2.5
Na (mg)	150	150
K (mg)	590	590
Cl (mg)	430	430
Ca (mg)	410	410
P (mg)	210	210
Mg (mg)	50	50
Mn (μg)	50	50
Se (μg)	13	13
Vitamin A (μg RE)	700	700
Vitamin D (μg)	10	10
Vitamin E (mg TE)	5.4	5.4
Vitamin K1 (μg)	54	54
Vitamin C (mg)	67	67
Vitamin B1 (mg)	0.47	0.47
Vitamin B2 (mg)	1	1
Niacin (mg)	6.7	6.7
Vitamin B6 (mg)	0.5	0.5
Folic acid (μg)	60	60

Pantothenic acid (mg)	3	3
Vitamin B12 (µg)	2	2
Biotin (µg)	15	15
Choline (mg)	67	67
Fe (mg)	8	8
I (µg)	100	100
Cu (mg)	0.4	0.4
Zn (mg)	5	5

Table III

Example 3

An example of a nutritional system in accordance with the invention is given in table IX.

	Up to 1 month of age	1 month to 2 months of age		3 to 6 months of ages
	Gender neutral	F	M	Gender neutral
Ingredients	Per Litre	Per Litre		Per Litre
Energy (kcal)	670	670	670	670
Protein (g)	9.1	9.1	9.1	14.1
Arginine (Free or protein bound) (g)	0.096	0.081	0.074	0.11
Fat (g)	35.7	35.7	35.7	35.7
Linoleic acid (g)	5.3	5.3	5.3	5.3
α-Linolenic acid (mg)	675	675	675	675
Lactose (g)	74.7	74.7	74.7	74.7
Prebiotic (100% GOS) (g)	4.3	4.3	4.3	4.3
Minerals (g)	2.5	2.5	2.5	2.5
Na (mg)	150	150	150	150
K (mg)	590	590	590	590
Cl (mg)	430	430	430	430
Ca (mg)	410	410	410	410
P (mg)	210	210	210	210
Mg (mg)	50	50	50	50

Mn (μg)	50	50	50	50
Se (μg)	13	13	13	13
Vitamin A (μg RE)	700	700	700	700
Vitamin D (μg)	10	10	10	10
Vitamin E (mg TE)	5.4	5.4	5.4	5.4
Vitamin K1 (μg)	54	54	54	54
Vitamin C (mg)	67	67	67	67
Vitamin B1 (mg)	0.47	0.47	0.47	0.47
Vitamin B2 (mg)	1	1	1	1.0
Niacin (mg)	6.7	6.7	6.7	6.7
Vitamin B6 (mg)	0.5	0.5	0.5	0.50
Lactoferrin (bovine) g	1	1	1	1.0
Folic acid (μg)	60	60	60	60
Pantothenic acid (mg)	3	3	3	3
Vitamin B12 (μg)	2	2	2	2
Biotin (μg)	15	15	15	15
Choline (mg)	67	67	67	67
Fe (mg)	8	8	8	8
I (μg)	100	100	100	100
Cu (mg)	0.4	0.4	0.4	0.4
Zn (mg)	5	5	5	5

Table IX

Claims

1. A gender specific synthetic nutritional composition for an infant 1 to 2 months of age wherein, the concentration of arginine is adapted based on that found in human milk produced for an infant of the same gender and age.
2. A gender specific synthetic nutritional composition according to claim 1 wherein, if the concentration of arginine is adapted to a male infant it is 47.4 to 142.3, mg per 100g and, if the concentration of arginine is adapted to a female infant it is 49.1 to 142.3, mg per 100g.
3. A composition according to claims 1 or 2 wherein, the gender specific synthetic nutritional composition is selected from the groups consisting of: infant formula, human milk and a composition for infants that is intended to be added to or diluted with human milk.
4. A method of preparing a composition as defined in any one of claims 1 to 3 comprising: measuring out an appropriate amount of a gender neutral synthetic nutritional composition and mixing it with an additive and/or diluent.
5. A nutritional system comprising a gender specific synthetic nutritional composition as defined in any one of claims 1 to 3.
6. A nutritional system according to claim 5 comprising one gender specific synthetic nutritional composition for a male infant of 1 to 2 months of age as defined in claim 1 or 2 and, one gender specific nutritional composition for a female infant of 1 to 2 months of age as defined in claim 1 or 2 wherein, the concentration of arginine in the synthetic nutritional composition for a female infant is higher than in that for the male.
7. A nutritional system according to claim 5 or 6 further comprising gender specific synthetic nutritional compositions for infants of up to 1 month of age and/or more than

2 months of age wherein, the concentration of arginine in said gender specific synthetic nutritional compositions does not differ by gender for infants of the same age.

8. A nutritional system according to any one of claims 5 to 7 further comprising gender neutral synthetic nutritional compositions for infants of up to 1 month of age and/or more than 2 months of age .
9. Use of a gender specific synthetic nutritional composition as defined in anyone of claims 1 to 3 to provide an optimum amount of arginine to a male or female infant, in particular an infant of 1 to 2 months of age.
10. A gender specific synthetic nutritional composition as defined in anyone of claims 1 to 3 for use to treat, protect or mitigate sub optimal growth and development of an infant.
11. A method for providing an optimum amount of arginine to a male or female infant, in particular an infant of 1 to 2 months of age comprising:
    a. Optionally preparing a gender specific nutritional composition as defined in any one of claims 1 to 3 from a gender neutral synthetic nutritional composition;
    b. Feeding a gender neutral synthetic nutritional composition as defined in any one of claims 1 to 3 to an infant of 1 to 2 months of age.
12. A nutritional system as defined in anyone of claims 5 to 8 for use to treat, protect or mitigate sub optimal growth and development of an infant.
13. A kit for providing an optimized amount of arginine to an infant, in particular an infant of 1 to 2 months age, the kit comprising:
    a. A gender neutral synthetic nutritional composition
    b. A label indicating dosage requirements for an infant so as to arrive at a gender specific nutritional composition as defined in any one of claims 1 to 3.

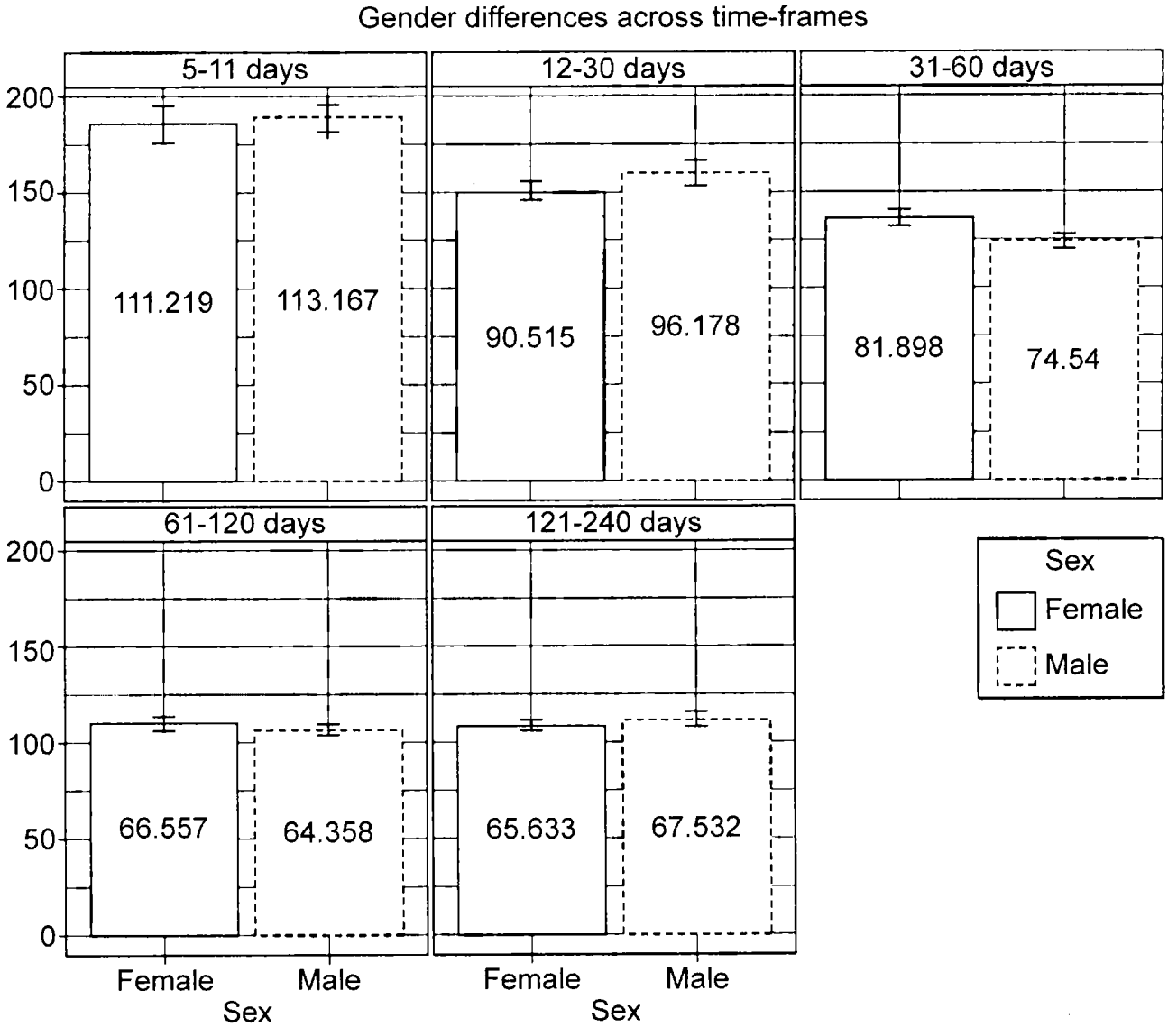
Gender differences across time-frames
5-11 days
12-30 days
31-60 days
61-120 days
121-240 days
200
150
100
50
0
111.219
113.167
90.515
96.178
81.898
74.54
66.557
64.358
65.633
67.532
Female
Male
Sex
Sex
Female
Male

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2015/076035

A. CLASSIFICATION OF SUBJECT MATTER

A23L 1/29(2006.01)i; A23C 9/00(2006.01)i

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; A23C

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 practicable, search terms used)

CPRSABS;EPONPL;CNABS;IPCOM;CNTXT;CJFD;DWPI;GOOGLE SCHOLAR:gender, infant, sex, formula, composition, milk, breast, human, arginine, male, female, month

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Stam J, et al., . "Can we define an infant's need from the composition of human milk?, " *The American Journal of Clinical Nutrition*, , Vol. (2), No. Vol.98, 10 July 2013 (2013-07-10), 521s-528s	1-13
A	WO 2006026879 A1 (MEDELA HOLDING AGET AL.) 16 March 2006 (2006-03-16) the whole document	1-13
A	CN 1280788 A (BAOYING CO LTD) 24 January 2001 (2001-01-24) the whole document	1-13

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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
17 June 2015	**03 July 2015**
Name and mailing address of the ISA/CN **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088, China** Facsimile No. **(86-10)62019451**	Authorized officer **ZHAO,Shihua** Telephone No. **(86-10)62411183**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2015/076035

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
WO 2006026879 A1	16 March 2006	CN 101014856 A	08 August 2007
		CN 101014856 B	27 June 2012
		JP 2008512656 A	24 April 2008
		AU 2005282183 A1	16 March 2006
		US 2008118615 A1	22 May 2008
CN 1280788 A	24 January 2001	None	