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

(57) Abstract: Gender specific synthetic nutritional compositions for infants up to 1 month of age wherein, the caseins content is adapted based on that found in HM produced for an infant of the same gender and age, and nutritional systems comprising them.

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, existence of certain conditions may not be in the best interests of the infant and it may contraindicate breastfeeding (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 aim to replicate those of human milk. However, replicating HM is not a simple task. HM not only contain numerous components, its composition 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 or how they vary e.g. by stage of lactation and/or gender.

Surprisingly it has now been identified that up to 1 month, more particularly 2 weeks to 1 month, postpartum, there is a difference in the caseins concentration range found in HM produced by mother's to girls in comparison to mother's 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 up to 1 month, more particularly 2 weeks to 1 month, postpartum, the mean caseins concentration of HM produced by mothers to boys was higher than that produced for mothers to girls.

Because these gender differences in the caseins concentration in HM have never been previously identified, they are not reflected in the compositions of synthetic nutritional compositions available today. Further, because these gender differences were not known. There was no incentive for gender specific synthetic nutritional compositions comprising caseins within a range identified for a particular gender to be developed

Caseins are proteins. An optimum protein intake helps to ensure optimum growth and development in infants. Further, optimum intake of proteins has been linked to a host of health benefits e.g. optimized immune functions, better gut maturation, optimum growth and development physically and cognitively, and a lower risk of obesity and cardiovascular disease. Further still, because of their calcium and phosphorus sequestration properties, caseins and/or the intermediates and/or products of their digestion have also been linked to a lower risk of calcium and phosphorus deficiencies, a lower risk of osteoporosis or low bone density, and optimum dental health.

Optimum growth and development and/or health benefits may be immediate and/or long term. Long term health benefits 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, respect to the caseins concentration, found in HM up to 1 month, more particularly 2 weeks to 1 month, 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 caseins concentration range in HM varies up to 1 month, more particularly 2 weeks to 1 month, 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 these identified gender differences. Prior to aforementioned findings the skilled

person has not incentive to develop such gender specific synthetic nutritional compositions or to include them in nutritional systems.

The caseins concentration in the gender specific synthetic nutritional compositions of the invention, and nutritional systems comprising them, more accurately reflect the caseins 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 caseins concentration to an infant of up to 1 month of age, more particularly 2 weeks to 1 month of age.

Optionally 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 caseins concentration intake helps to ensure optimum growth and development in infants, the gender specific synthetic nutritional compositions, and nutritional systems of the invention, can also be used to treat, prevent or mitigate sub optimal growth and development e.g. obesity in 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 caseins concentration in HM does not differ (higher or lower) by gender 1 month or later 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 more than 1 month of age wherein, the caseins concentration 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 up to 12months old, up to 9 months old, up to 8months old, up to 6 month old.

Drawings

FIG.1 is a graphical representation of the identified difference in the mean caseins concentration 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 4 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 different min and max ranges for the concentration of caseins by gender. Surprisingly, the results of this study also indicated that that up to 1 month, more particularly 2 weeks to 1 month, postpartum, there is a difference in the mean caseins concentration 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 up to 1 month, particularly 2 weeks to 1 month, of age wherein, the caseins concentration 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.

Appropriate types of gender specific synthetic nutritional compositions are dependent on age. 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 up to 1 month of age wherein, the caseins concentration is adapted based on that found in HM produced for an infant of the same gender and age.

The gender specific synthetic nutritional composition can be a male specific synthetic nutritional composition or a female specific synthetic nutritional composition for an infant up to 1 month of age, more particularly 2 weeks to 1 month of age.

In an embodiment the gender specific synthetic nutritional composition is a male specific synthetic nutritional composition for an infant of up to 1 month of age, more particularly 2 weeks to 1 month of age, and comprises a caseins concentration of 3598.2mg to 10512.2mg, 5228.81mg to 10462.73mg, 3484.17mg to 8718.09mg, 6509.2 to 10512.2, or 6973.45mg, per L.

The total protein content of the gender specific synthetic nutritional compositions of the invention is expressed in g/100mL. This may refer to the total protein content of a reconstituted gender specific synthetic nutritional composition.

In an embodiment the gender specific synthetic nutritional composition is a female specific synthetic nutritional composition for an infant of up to 1 month of age, more particularly 2 weeks to 1 month of age, and comprises a caseins concentration of 1118.3mg to 9509.9mg, 2195.86mg to 9509.9mg, 4120.4mg to 7969.48mg 1118.3 to 6509.15, or 6044.94mg, per L.

The caseins concentration can be measured by methods well known in the art. In particular caseins concentration can be measured by direct or indirect Kjeldahl nitrogen determination as

described by AOAC (AOAC official method 991.20, 991.22, 991.23; Lynch et al (1998) *J AOAC Int* 81: 763).

The caseins concentration is the combined total of the concentrations of any specific type of casein. Non limiting examples include: alpha-S1-casein, alpha-S2-casein (bovine only), beta-casein, and kappa casein.

Any source of caseins 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. Non limiting examples include: bovine & buffalo caseins, human caseins, goat caseins, sheep caseins, and combinations thereof.

The caseins 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 proteins, carbohydrates, oligosaccharides, lipids, prebiotics or probiotics, essential fatty acids, nucleotides, nucleosides, vitamins, minerals and other micronutrients.

Non limiting examples of other proteins include, 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 any mixtures of the foregoing

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. 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 or, 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. A protein source (including caseins), 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 1 10^0C 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 in 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 a 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 caseins 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 up to 1 month of age, more particularly 2 weeks to 1 month of

age, and a gender specific synthetic nutritional composition for a female infant of up to 1 month of age, more particularly 2 weeks to 1 month of age.

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

The caseins concentration in the male gender synthetic nutritional compositions may be higher by any amount.

In an embodiment the ratio of the caseins concentration between the female gender specific nutritional composition and male gender specific synthetic nutritional composition is 1:9.4 to 1:1.000031, 1:9.4 to 1:1.11; or 1:3.22 to 1:1.15.

In an embodiment the male gender specific synthetic nutritional composition contains 0.001mg to 9393.9mg, 0.2mg to 9393.9mg, 928mg to 2480mg, or 928.51mg to 1002.3mg, per L more caseins than the female gender specific synthetic nutritional composition.

In addition to that disclosed hereinabove, the referenced study further indicated that between 31 days and 240 days postpartum there is no difference in the mean caseins concentration 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 more than 1 month of age wherein, the caseins concentration 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 more than 1 month of age.

Non limiting examples of ages, or ranges thereof, more than 1 month, include: 1-2mths, 2mth, 2-4mths, 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 caseins concentration in HM found by gender at one or more stages of lactation. As stated herein, optimum caseins concentration intake helps to ensure optimum growth and development in infants, and has been linked to a host of immediate and long term health benefits e.g. optimized immune functions, better gut maturation, optimum growth and development physically and cognitively, a lower risk of obesity and cardiovascular disease in childhood and later life, a lower risk of calcium and

phosphorus deficiencies, a lower risk of osteoporosis or low bone density, and optimum dental health.

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 and development e.g. obesity, of an infant..

A gender specific synthetic nutritional composition may to provide an optimum amount of caseins concentration to an infant up to 1 month of age, more particularly 2 weeks to 1 month of age.

The nutritional system may provide an optimum amount of caseins concentration to 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 caseins concentration to an infant up to 1 month of age, more particularly 2 weeks to 1 month of age comprising:

a) Optionally preparing a gender specific synthetic nutritional compositions 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 up to 1 month of age, more particularly 2 weeks to 1 month 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 caseins to an infant up to 1 month of age, more particularly 2 weeks to 1 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 caseins concentration in HM samples collected from mothers to either male or females 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 caseins concentration in the HM samples collected as part of the above detailed study were analysed using a LabChip GX II gel electrophoresis system from Perkin Elmer according to the manufacturer's protocols. It's a microfluidic chip-based gel electrophoresis system that separates and quantifies proteins similar to polyacrylamide gel electrophoresis (PAGE) with the advantage of automated high-throughput 96-well plate capacity. Purified bovine caseins were used to generate a calibration curve (all partially separated casein peaks integrated as one unique peak) for precise quantification of the human caseins.

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

Caseins concentration mg/L								
	Female					Male		
Stage	Min	Mean	SD	Max	Min	Mean	SD	Max
5 to 11 days	1814.2	5864.57	2242.08	9971.9	1634.2	5777.30	2184.79	11297.7
2 weeks to 1 month	1118.3	6044.94	1924.54	9509.9	3598.2	6973.45	1744.64	10512.2
1 to 2 months	3269.1	6136.88	1682.96	10448.4	4284.6	6459.66	1436.45	10448.4
2 to 4 months	3132.4	5578.48	1224.41	8199.9	2049.7	5790.48	1523.90	8963.6
4 to 8 months	2907.0	5438.93	1261.37	8634.5	2415.1	5704.90	1231.49	8634.5

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 +

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 caseins

Timeframe	Variable	Estimate	lower	Upper	Pvalue
5 to 11 days	caseins	158.914	-551.149	868.977	0.6602333
2 weeks to 1 month	caseins	-887.785	-1611.268	-164.301	0.0162913
1 to 2 months	caseins	-256.157	-969.340	457.026	0.4805864
2 to 4 months	caseins	-212.003	-922.131	498.125	0.5576464
4 to 8 months	caseins	-144.886	-860.015	570.243	0.6906632

Table II

A P-value inferior to 0.1 for a particular timeframe suggests that there is a statistically significant difference in the caseins 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 mean caseins concentration between HM produced for male and female infants was identified at 2

weeks to 1 month postpartum. No statistically significant difference was identified in the mean caseins concentration between HM produced for male and female infants older than 30 days postpartum Viz. 1 to 2 months, 2 to 4 months and 4 to 8 months.

Example 2

Examples of gender specific infant formulas are given in table III

	2 weeks to 1 month of age		Up to one month of age	
	F	M	F	M
Ingredients	Per Litre		Per Litre	
Energy (kcal)	670	670	670	670
Protein (g)	10.01 including caseins in a concentration of 6.04g	10.8 including caseins in a concentration of 6.97g	10.01 including caseins in a concentration of 6.04g	10.8 including caseins in a concentration of 6.97g
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
Niacin (mg)	6.7	6.7	6.7	6.7
Vitamin B6 (mg)	0.5	0.5	0.5	0.5
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 III

Example 3

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

	Up to one month of age		1 to 2 months of ages of age
	F	M	Gender neutral
Ingredients	Per Litre		Per Litre
Energy (kcal)	670	670	670
Protein (g)	10.01 including caseins in a concentration of 6.04g	10.8 including caseins in a concentration of 6.97g	9.1 including caseins in a concentration of Ca. 5.8g
Fat (g)	35.7	35.7	35.7
Linoleic acid (g)	5.3	5.3	5.3
α-Linolenic acid (mg)	675	675	675

Lactose (g)	74.7	74.7	74.7
Prebiotic (100% GOS) (g)	4.3	4.3	4.3
Minerals (g)	2.5	2.5	2.5
Na (mg)	150	150	150
K (mg)	590	590	590
Cl (mg)	430	430	430
Ca (mg)	410	410	410
P (mg)	210	210	210
Mg (mg)	50	50	50
Mn (µg)	50	50	50
Se (µg)	13	13	13
Vitamin A (µg RE)	700	700	700
Vitamin D (µg)	10	10	10
Vitamin E (mg TE)	5.4	5.4	5.4
Vitamin K1 (µg)	54	54	54
Vitamin C (mg)	67	67	67
Vitamin B1 (mg)	0.47	0.47	0.47
Vitamin B2 (mg)	1	1	1
Niacin (mg)	6.7	6.7	6.7
Vitamin B6 (mg)	0.5	0.5	0.5
Lactoferrin (bovine) g	1	1	1
Folic acid (µg)	60	60	60
Pantothenic acid (mg)	3	3	3
Vitamin B12 (µg)	2	2	2
Biotin (µg)	15	15	15
Choline (mg)	67	67	67
Fe (mg)	8	8	8
I (µg)	100	100	100
Cu (mg)	0.4	0.4	0.4
Zn (mg)	5	5	5

Table IV

Claims

1. A gender specific synthetic nutritional composition for an infant up to 1 month of age, wherein, the caseins concentration 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, the caseins concentration is adapted to a male infant and is 3598.2mg to 10512.2mg per L.
3. A gender specific synthetic nutritional composition according to claim 1 wherein, the caseins concentration is adapted to a female infant and is 1118.3mg to 9509.9mg per L.
4. A composition according to anyone of claims 1 to 3 wherein, the gender specific synthetic nutritional composition is selected from the groups consisting of; infant formula, and a composition for infants that is intended to be added to or diluted with human milk.
5. A method of preparing a composition as defined in any one of claims 1 to 4 comprising: measuring out an appropriate amount of a gender neutral synthetic nutritional composition and mixing it with an additive and/or diluent.
6. A nutritional system comprising a gender specific synthetic nutritional composition as defined in any one of claims 1 to 4.
7. A nutritional system according to claim 6 comprising a gender specific synthetic nutritional composition for a male infant as defined in claim 2 and, a gender specific nutritional compositions for a female infant as defined in claim 3.
8. A nutritional system according to claim 7 wherein the caseins concentration in said male gender specific synthetic nutritional composition is higher than that of said female gender specific synthetic nutritional composition.
9. A nutritional system according to any one of claims 6 to 8 further comprising gender specific synthetic nutritional compositions for infants of more than 1 month of age wherein, the caseins concentration does not differ by gender for infants of the same age.
10. A nutritional system according to any one of claims 6 to 9 further comprising gender neutral synthetic nutritional compositions for infants of more than 1 month of age.

11. Use of a gender specific synthetic nutritional composition as defined in anyone of claims 1 to 4 to provide an optimum amount of caseins to an infant of up to one month of age.
12. A gender specific synthetic nutritional composition as defined in anyone of claims 1 to 4 for use to treat, protect or mitigate sub optimal growth and development of an infant.
13. A method for providing an optimum amount of caseins to an infant of up to 1 month of age comprising;
    a. Optionally preparing a gender specific nutritional compositions as defined in any one of claims 1 to 4 from a gender neutral synthetic nutritional composition;
    b. Feeding a gender specific nutritional compositions as defined in any one of claims 1 to 4 to an infant up to 1 month of age.
14. A nutritional system as defined in anyone of claims 6 to 10 for use to treat, prevent or mitigate sub optimal growth and development of an infant.
15. A kit for providing an optimized amount of caseins to an infant of up to 1 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 as defined in anyone of claims 1 to 4.

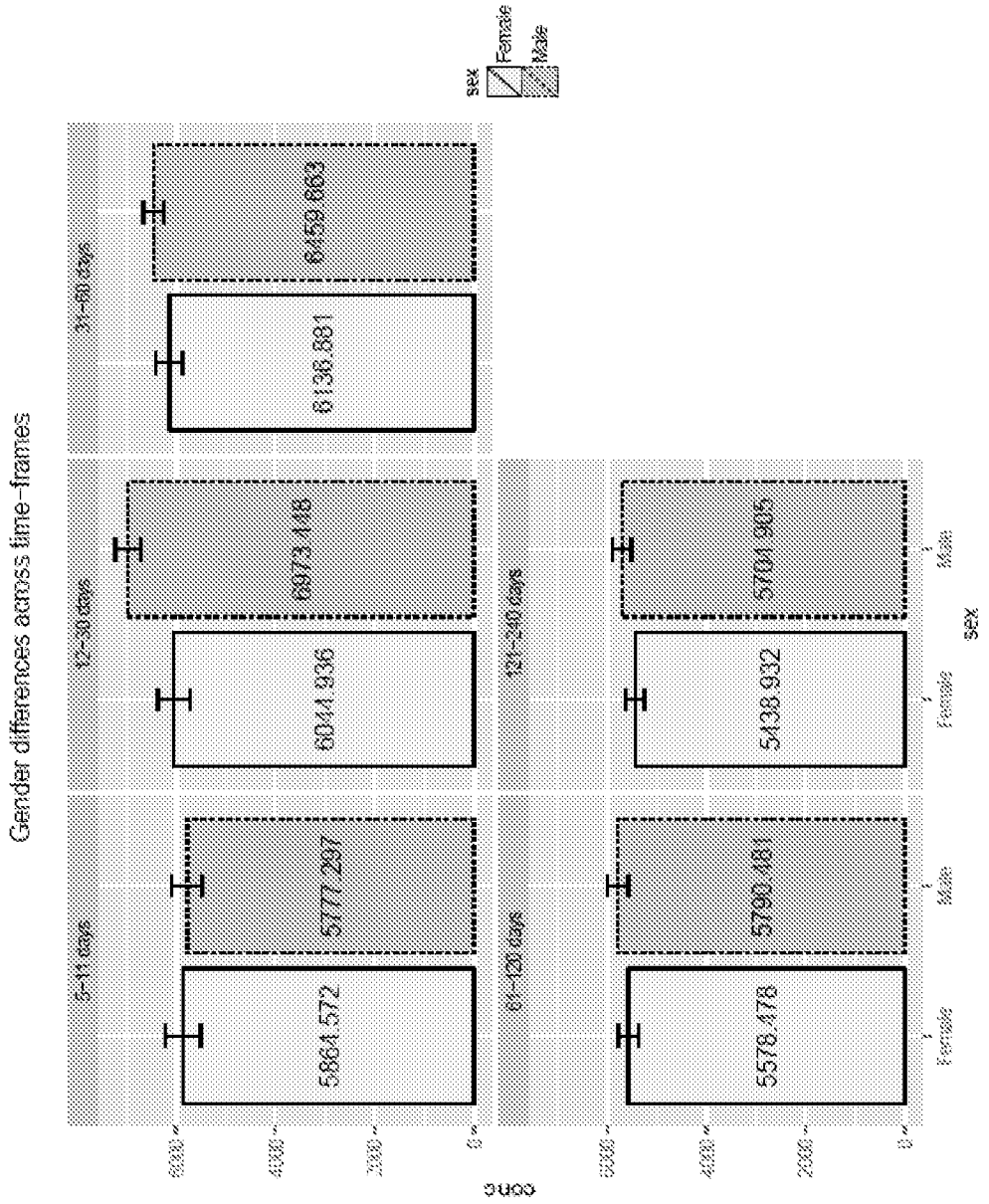
Gender differences across time-frames
sex
Female
Male
1-30 days
31-60 days
61-120 days
121-240 days
5864.572
5777.297
6044.936
6373.148
6138.881
6459.663
5578.478
5790.481
5438.932
5701.905
Female
Male
sex
count
0
2000
4000
6000

FIG. 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/075010

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)

USTXT;CNTXT;CNABS;WOTXT;VEN;EPTXT:gender, infant,fomula+, nutrition+ composition, sex+, male, female, mother+, girl, casein+, total protein, human milk, boy, NESTLE

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?" *American Journal of Clinical Nutrition,* No. vol. 98(suppl), 31 December 2013 (2013-12-31), pages 521S-528S	1, 4-6, 11, 13, 15
X	ALTUFAILY, Y. A. et al. "The effect of infant gender on the quality of breast milk." *Kufa Med. Journal,* Vol. no. 1, No. vol. 12, 31 December 2009 (2009-12-31), pages 435-440	1, 4-6, 11, 13, 15
A	THAKKAR, S. K. et al. "Dynamics of human milk nutrient composition of women from Singapore with a special focus on lipids." *American Journal of Human Biology,* No. vol. 25, 31 December 2013 (2013-12-31), pages 770-779	1-11, 13, 15
A	CN 1280788 A (BAOYING CO. LTD.) 24 January 2001 (2001-01-24) the whole document	1-11, 13, 15
A	CN 101313721 A (INNER MONGOLIA MENGNIU DAIRY IND. GROUP CO. LTD.) 03 December 2008 (2008-12-03) the whole document	1-11, 13, 15

☑ 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
15 December 2014	**08 January 2015**

Name and mailing address of the ISA/CN	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/075010

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008118615 A1 (MEDELA HOLDING AG.) 22 May 2008 (2008-05-22) the whole document	1-11, 13, 15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2014/075010

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **12, 14**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] Claims 12 and 14 are attributed to the methods for treatment of human or animal body by therapy. They do not meet the criteria set out in PCT Rules 39.1 (iv).

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2014/075010

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
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		CN 101014856 B	27 June 2012
		JP 2008512656 A	24 April 2008
		AU 2005282183 A1	16 March 2006
		WO 2006026879 A1	16 March 2006
		EP 1637880 A1	22 March 2006
		EP 1787114 A1	23 May 2007
		IN 200700425 P2	06 July 2007
CN 101313721 A	03 December 2008	CN 101313721 B	27 June 2012