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(54) Title: NUTRITIONAL COMPOSITIONS COMPRISING A CASEIN HYDROLYSATE, AS WELL AS DIETARY BUTYRATE AND/OR A COMPOUND FOR STIMULATING FORMATION OF ENDOGENOUS BUTYRATE

(57) Abstract: Provided are nutritional compositions including a component for stimulating butyrate production in the human gut and/or dietary butyrate. Further disclosed are methods of reducing allergic reaction and promoting tolerance to cow's milk allergy in a pediatric subject by providing said nutritional compositions to a target subject.

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DESCRIPTION

NUTRITIONAL COMPOSITIONS COMPRISING A CASEIN HYDROLYSATE, AS WELL AS DIETARY BUTYRATE AND/OR A COMPOUND FOR STIMULATING FORMATION OF ENDOGENOUS BUTYRATE

TECHNICAL FIELD

[0001] The present disclosure relates generally to nutritional compositions comprising dietary butyrate and a component, which can stimulate the production of endogenous butyrate. The nutritional compositions are suitable for administration to pediatric subjects. Additionally, the disclosure relates to nutritional compositions including a prebiotic comprising polydextrose and galacto-oligosaccharides, dietary butyrate, and a protein equivalent source. Further, disclosed are methods for reducing the incidence of allergy and/or improving tolerance to cow's milk allergy in target subjects. The disclosed nutritional compositions may provide additive and or/synergistic beneficial health effects.

BACKGROUND ART

[0002] Administration of nutritional compositions or other compositions including butyrate or butyrate derivatives often suffer from difficulties regarding the bioavailability of butyrate upon administration. For example, certain butyrate derivatives undergo degradation or oxidation, which ultimate affect the bioavailability of the butyrate derivative upon ingestion. As such, compositions including butyrate derivatives may not provide therapeutic efficacy upon ingestion given the degradation of the butyrate derivative.

[0003] Additionally, nutritional compositions including butyrate may suffer from poor palatability. The unpleasant taste and odor of compositions including butyrate can make the oral administration of certain nutritional compositions including butyrate difficult, especially in the pediatric population. For example, certain butyric acid derivatives at room temperature are present as a dense liquid having an unpleasant taste and intense odor.

[0004] Accordingly, it would be beneficial to provide a nutritional composition that includes endogenous butyrate to avoid the palatability issues sometimes found with dietary butyrate. Further, there is a need for palatable, safe, yet effective, nutritional compositions that include a combination of one or more prebiotics, a protein equivalent source, and butyrate to reduce incidence of allergy and increase tolerance to cow's milk allergy in certain subjects.

DISCLOSURE OF THE INVENTION

[0005] Briefly, the present disclosure is directed, in an embodiment, to a nutritional composition that includes dietary butyrate and a component which can stimulate the production of endogenous butyrate in the human gut. In some embodiments, the dietary butyrate may be encapsulated. In some embodiments, the endogenous butyrate may be

provided by stimulating short chain fatty acid ("SCFA") production by the gut microbiota and the dietary butyrate may be provided by an enriched lipid fraction derived from milk.

[0006] It is to be understood that both the foregoing general description and the following detailed description present embodiments of the disclosure and are intended to provide an overview or framework for understanding the nature and character of the disclosure as it is claimed. The description serves to explain the principles and operations of the claimed subject matter. Other and further features and advantages of the present disclosure will be readily apparent to those skilled in the art upon a reading of the following disclosure.

BEST MODE FOR CARRYING OUT THE INVENTION

[0007] Reference now will be made in detail to the embodiments of the present disclosure, one or more examples of which are set forth hereinbelow. Each example is provided by way of explanation of the nutritional composition of the present disclosure and is not a limitation. In fact, it will be apparent to those skilled in the art that various modifications and variations can be made to the teachings of the present disclosure without departing from the scope of the disclosure. For instance, features illustrated or described as part of one embodiment, can be used with another embodiment to yield a still further embodiment.

[0008] Thus, it is intended that the present disclosure covers such modifications and variations as come within the scope of the appended claims and their equivalents. Other objects, features and aspects of the present disclosure are disclosed in or are apparent from the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only and is not intended as limiting the broader aspects of the present disclosure.

[0009] The present disclosure relates generally to nutritional compositions comprising dietary butyrate and a component for stimulating the production of endogenous butyrate. Additionally, the disclosure relates to methods for improving the shelf stability and/or organoleptic properties of nutritional compositions including butyrate.

[0010] "Nutritional composition" means a substance or formulation that satisfies at least a portion of a subject's nutrient requirements. The terms "nutritional(s)", "nutritional formula(s)", "enteral nutritional(s)", and "nutritional supplement(s)" are used as non-limiting examples of nutritional composition(s) throughout the present disclosure. Moreover, "nutritional composition(s)" may refer to liquids, powders, gels, pastes, solids, concentrates, suspensions, or ready-to-use forms of enteral formulas, oral formulas, formulas for infants, formulas for pediatric subjects, formulas for children, growing-up milks and/or formulas for adults.

[0011] "Pediatric subject" means a human less than 13 years of age. In some embodiments, a pediatric subject refers to a human subject that is between birth and 8 years old. In other

embodiments, a pediatric subject refers to a human subject between 1 and 6 years of age. In still further embodiments, a pediatric subject refers to a human subject between 6 and 12 years of age. The term "pediatric subject" may refer to infants (preterm or fullterm) and/or children, as described below.

[0012] "Infant" means a human subject ranging in age from birth to not more than one year and includes infants from 0 to 12 months corrected age. The phrase "corrected age" means an infant's chronological age minus the amount of time that the infant was born premature. Therefore, the corrected age is the age of the infant if it had been carried to full term. The term infant includes low birth weight infants, very low birth weight infants, and preterm infants. "Preterm" means an infant born before the end of the 37th week of gestation. "Full term" means an infant born after the end of the 37th week of gestation.

[0013] "Child" means a subject ranging in age from 12 months to about 13 years. In some embodiments, a child is a subject between the ages of 1 and 12 years old. In other embodiments, the terms "children" or "child" refer to subjects that are between one and about six years old, or between about seven and about 12 years old. In other embodiments, the terms "children" or "child" refer to any range of ages between 12 months and about 13 years.

[0014] "Infant formula" means a composition that satisfies at least a portion of the nutrient requirements of an infant. In the United States, the content of an infant formula is dictated by the federal regulations set forth at 21 C.F.R. Sections 100, 106, and 107.

[0015] The term "medical food" refers enteral compositions that are formulated or intended for the dietary management of a disease or disorder. A medical food may be a food for oral ingestion or tube feeding (nasogastric tube), may be labeled for the dietary management of a specific medical disorder, disease or condition for which there are distinctive nutritional requirements, and may be intended to be used under medical supervision.

[0016] The term "peptide" as used herein describes linear molecular chains of amino acids, including single chain molecules or their fragments. The peptides described herein include no more than 50 total amino acids. Peptides may further form oligomers or multimers consisting of at least two identical or different molecules. Furthermore, peptidomimetics of such peptides where amino acid(s) and/or peptide bond(s) have been replaced by functional analogs are also encompassed by the term "peptide". Such functional analogues may include, but are not limited to, all known amino acids other than the 20 gene-encoded amino acids such as selenocysteine.

[0017] The term "peptide" may also refer to naturally modified peptides where the modification is effected, for example, by glycosylation, acetylation, phosphorylation and similar modification which are well known in the art. In some embodiments, the peptide

component is distinguished from a protein source also disclosed herein. Further, peptides may, for example, be produced recombinantly, semi-synthetically, synthetically, or obtained from natural sources such as after hydrolysation of proteins, including but not limited to casein, all according to methods known in the art.

[0018] The term "molar mass distribution" when used in reference to a hydrolyzed protein or protein hydrolysate pertains to the molar mass of each peptide present in the protein hydrolysate. For example, a protein hydrolysate having a molar mass distribution of greater than 500 Daltons means that each peptide included in the protein hydrolysate has a molar mass of at least 500 Daltons. Accordingly, in some embodiments, the peptides disclosed in Table 1 and Table 2 are derived from a protein hydrolysate having a molar mass distribution of greater than 500 Daltons. To produce a protein hydrolysate having a molar mass distribution of greater than 500 Daltons, a protein hydrolysate may be subjected to certain filtering procedures or any other procedure known in the art for removing peptides, amino acids, and/or other proteinaceous material having a molar mass of less than 500 Daltons. For the purposes of this disclosure, any method known in the art may be used to produce the protein hydrolysate having a molar mass distribution of greater than 500 Dalton.

[0019] The term "protein equivalent" or "protein equivalent source" includes any protein source, such as soy, egg, whey, or casein, as well as non-protein sources, such as peptides or amino acids. Further, the protein equivalent source can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, peptides, amino acids, and the like. Bovine milk protein sources useful in practicing the present disclosure include, but are not limited to, milk protein powders, milk protein concentrates, milk protein isolates, nonfat milk solids, nonfat milk, nonfat dry milk, whey protein, whey protein isolates, whey protein concentrates, sweet whey, acid whey, casein, acid casein, caseinate (*e.g.* sodium caseinate, sodium calcium caseinate, calcium caseinate), soy bean proteins, and any combinations thereof. The protein equivalent source can, in some embodiments comprise hydrolyzed protein, including partially hydrolyzed protein and extensively hydrolyzed protein. The protein equivalent source may, in some embodiments, include intact protein. More particularly, the protein source may include a) about 20% to about 80% of the peptide component described herein, and b) about 20% to about 80 % of an intact protein, a hydrolyzed protein, or a combination thereof.

[0020] The term "protein equivalent source" also encompasses free amino acids. In some embodiments, the amino acids may comprise, but are not limited to, histidine, isoleucine, leucine, lysine, methionine, cysteine, phenylalanine, tyrosine, threonine, tryptophan, valine, alanine, arginine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, proline, serine, carnitine, taurine and mixtures thereof. In some embodiments, the amino acids may be

branched chain amino acids. In certain other embodiments, small amino acid peptides may be included as the protein component of the nutritional composition. Such small amino acid peptides may be naturally occurring or synthesized.

[0021] "Fractionation procedure" includes any process in which a certain quantity of a mixture is divided up into a number of smaller quantities known as fractions. The fractions may be different in composition from both the mixture and other fractions. Examples of fractionation procedures include but are not limited to, melt fractionation, solvent fractionation, supercritical fluid fractionation and/or combinations thereof.

[0022] The term "essential amino acid" as used herein refers to an amino acid that cannot be synthesized *de novo* by the organism being considered or that is produced in an insufficient amount, and therefore must be supplied by diet. For example, in some embodiments, where the target subject is a human, an essential amino acid is one that cannot be synthesized *de novo* by a human.

[0023] The term "non-essential amino acid" as used herein refers to an amino acid that can be synthesized by the organism or derived by the organism from essential amino acids. For example, in some embodiments, where the target subject is a human, a non-essential amino acid is one that can be synthesized in the human body or derived in the human body from essential amino acids.

[0024] "Milk fat globule membrane" includes components found in the milk fat globule membrane including but not limited to milk fat globule membrane proteins such as Mucin 1, Butyrophilin, Adipophilin, CD36, CD14, Lactadherin (PAS6/7), Xanthine oxidase and Fatty Acid binding proteins etc.

[0025] The term "growing-up milk" refers to a broad category of nutritional compositions intended to be used as a part of a diverse diet in order to support the normal growth and development of a child between the ages of about 1 and about 6 years of age.

[0026] "Milk" means a component that has been drawn or extracted from the mammary gland of a mammal. In some embodiments, the nutritional composition comprises components of milk that are derived from domesticated ungulates, ruminants or other mammals or any combination thereof.

[0027] "Nutritionally complete" means a composition that may be used as the sole source of nutrition, which would supply essentially all of the required daily amounts of vitamins, minerals, and/or trace elements in combination with proteins, carbohydrates, and lipids. Indeed, "nutritionally complete" describes a nutritional composition that provides adequate amounts of carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals and energy required to support normal growth and development of a subject.

[0028] A nutritional composition that is "nutritionally complete" for a full term infant will, by definition, provide qualitatively and quantitatively adequate amounts of all carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals, and energy required for growth of the full term infant.

[0029] A nutritional composition that is "nutritionally complete" for a child will, by definition, provide qualitatively and quantitatively adequate amounts of all carbohydrates, lipids, essential fatty acids, proteins, essential amino acids, conditionally essential amino acids, vitamins, minerals, and energy required for growth of a child.

[0030] "Exogenous butyrate" or "dietary butyrate" each refer to butyrate or butyrate derivatives which are intentionally included in the nutritional composition of the present disclosure itself, rather than generated in the gut.

[0031] "Endogenous butyrate" or "butyrate from endogenous sources" each refer to butyrate present in the gut as a result of ingestion of the disclosed composition that is not added as such, but is present as a result of other components or ingredients of the composition; the presence of such other components or ingredients of the composition stimulates butyrate production in the gut.

[0032] The term "cow's milk allergy" describes a food allergy, *i.e.* an immune adverse reaction to one or more of the proteins contained in cow's milk in a human subject. The principal symptoms are gastrointestinal, dermatological, and respiratory symptoms. These can translate into skin rashes, hives, vomiting, diarrhea, constipation and distress. The clinical spectrum extends to diverse disorders: anaphylactic reactions, atopic dermatitis, wheeze, infantile colic, gastro esophageal reflux disease (GERD), esophagitis, colitis gastroenteritis, headache/migraine and constipation.

[0033] The nutritional composition of the present disclosure may be substantially free of any optional or selected ingredients described herein, provided that the remaining nutritional composition still contains all of the required ingredients or features described herein. In this context, and unless otherwise specified, the term "substantially free" means that the selected composition may contain less than a functional amount of the optional ingredient, typically less than 0.1% by weight, and also, including zero percent by weight of such optional or selected ingredient.

[0034] All percentages, parts and ratios as used herein are by weight of the total composition, unless otherwise specified.

[0035] All references to singular characteristics or limitations of the present disclosure shall include the corresponding plural characteristic or limitation, and vice versa, unless otherwise specified or clearly implied to the contrary by the context in which the reference is made.

[0036] All combinations of method or process steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0037] The methods and compositions of the present disclosure, including components thereof, can comprise, consist of, or consist essentially of the essential elements and limitations of the embodiments described herein, as well as any additional or optional ingredients, components or limitations described herein or otherwise useful in nutritional compositions.

[0038] As used herein, the term "about" should be construed to refer to both of the numbers specified as the endpoint(s) of any range. Any reference to a range should be considered as providing support for any subset within that range.

[0039] The present disclosure is directed to nutritional compositions including butyrate and LGG. Non-limiting examples of butyrate for use herein include butyric acid, butyrate salts, and glycerol esters of butyric acid. The nutritional compositions may further include a carbohydrate source, a protein source, and a fat or lipid source. In some embodiments, the nutritional compositions may include a component capable of stimulating endogenous butyrate production; in other embodiments, the nutritional compositions may include both dietary and endogenous butyrate.

[0040] The benefit to providing both exogenous and endogenous butyrate is accelerated tolerance acquisition towards cow's milk. Additionally, the benefit to providing both exogenous and endogenous butyrate together with *Lactobacillus rhamnoses* GG ("LGG") is accelerated tolerance acquisition toward cow's milk. Conventional dietary management of cow's milk allergy includes the use of formulations containing protein hydrolysates and amino acids rather than intact proteins, and certain probiotics such as Lactobacillus rhamnoses GG ("LGG"), which contribute to accelerated tolerance acquisition towards cow's milk. The inclusion of a component to stimulate endogenous butyrate production by the gut microbiota may further accelerate tolerance acquisition and/or may be applied as a functional replacement of LGG in a nutritional composition. Further, the inclusion of certain probiotics, such as LGG in combination with butyrate, either endogenous or exogenous butyrate, can contribute to accelerated tolerance acquisition towards cow's milk.

[0041] In an embodiment, the component for stimulating endogenous buyrate is a prebiotic comprising both polydextrose ("PDX") and galacto-oligosaccharides ("GOS"). A prebiotic component including PDX and GOS can enhance endogenous butyrate production by microbiota. Butyrate has epigenetic (histone deacetylase inhibition activity) that results in regulatory responses such as generation of regulatory T-cells. In the context of cow s milk

allergy, these regulatory responses may result in accelerated tolerance acquisition to cow's milk protein.

[0042] In addition to PDX and GOS, the nutritional composition may also contain one or more other prebiotics which can exert additional health benefits, which may include, but are not limited to, selective stimulation of the growth and/or activity of one or a limited number of beneficial gut bacteria, stimulation of the growth and/or activity of ingested probiotic microorganisms, selective reduction in gut pathogens, and favorable influence on gut short chain fatty acid profile. Such prebiotics may be naturally-occurring, synthetic, or developed through the genetic manipulation of organisms and/or plants, whether such new source is now known or developed later. Prebiotics useful in the present disclosure may include oligosaccharides, polysaccharides, and other prebiotics that contain fructose, xylose, soya, galactose, glucose and mannose.

[0043] More specifically, prebiotics useful in the present disclosure include PDX and GOS, and can, in some embodiments, also include, polydextrose powder, lactulose, lactosucrose, raffinose, gluco-oligosaccharide, inulin, fructo-oligosaccharide (FOS), isomalto-oligosaccharide, soybean oligosaccharides, lactosucrose, xylo-oligosaccharide (XOS), chito-oligosaccharide, manno-oligosaccharide, aribino-oligosaccharide, siallyl-oligosaccharide, fuco-oligosaccharide, and gentio-oligosaccharides.

[0044] In an embodiment, the total amount of prebiotics present in the nutritional composition may be from about 1.0 g/L to about 10.0 g/L of the composition. More preferably, the total amount of prebiotics present in the nutritional composition may be from about 2.0 g/L and about 8.0 g/L of the composition. In some embodiments, the total amount of prebiotics present in the nutritional composition may be from about 0.01 g/100 Kcal to about 1.5 g/100 Kcal. In certain embodiments, the total amount of prebiotics present in the nutritional composition may be from about 0.15 g/100 Kcal to about 1.5 g/100 Kcal. In some embodiments, the prebiotic component comprises at least 20% w/w PDX and GOS.

[0045] The amount of PDX in the nutritional composition may, in an embodiment, be within the range of from about 0.015 g/100 Kcal to about 1.5 g/100 Kcal. In another embodiment, the amount of polydextrose is within the range of from about 0.2 g/100 Kcal to about 0.6 g/100 Kcal. In some embodiments, PDX may be included in the nutritional composition in an amount sufficient to provide between about 1.0 g/L and 10.0 g/L. In another embodiment, the nutritional composition contains an amount of PDX that is between about 2.0 g/L and 8.0 g/L. And in still other embodiments, the amount of PDX in the nutritional composition may be from about 0.05 g/100 Kcal to about 1.5 g/100 Kcal.

[0046] The prebiotic component also comprises GOS. The amount of GOS in the nutritional composition may, in an embodiment, be from about 0.015 g/100 Kcal to about 1.0 g/100

Kcal. In another embodiment, the amount of GOS in the nutritional composition may be from about 0.2 g/100 Kcal to about 0.5 g/100 Kcal.

[0047] In a particular embodiment, GOS and PDX are supplemented into the nutritional composition in a total amount of at least about 0.015 g/100 Kcal or about 0.015 g/100 Kcal to about 1.5 g/100 Kcal. In some embodiments, the nutritional composition may comprise GOS and PDX in a total amount of from about 0.1 to about 1.0 g/100 Kcal.

[0048] In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 5 g/100 Kcal to about 500 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 15 g/100 Kcal to about 450 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 20 g/100 Kcal to about 400 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 25 g/100 Kcal to about 350 g/100 kcal. In some embodiments, the nutritional composition includes a source of dietary butyrate that is present in an amount of from about 30 g/100 Kcal to about 280 g/100 kcal.

[0049] In some embodiments, the nutritional composition includes from about 0.01 g to about 10 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.1 g to about 8 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.4 g to about 7 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 0.7 g to about 6.5 g of dietary butyrate per 100 g of total fat in the nutritional composition. In some embodiments, the nutritional composition includes from about 1.2 g to about 5.1 g of dietary butyrate per 100 g of total fat in the nutritional composition.

[0050] In some embodiments the dietary butyrate is provided by one or more of the following: butyric acid; butyrate salts, including sodium butyrate, potassium butyrate, calcium butyrate, and/or magnesium butyrate; glycerol esters of butyric acid; and/or corresponding mixtures and corresponding salts of pharmaceutically acceptable bases or acids, pure diastereoisomeric forms and enantiomeric forms or mixtures thereof.

[0051] The dietary butyrate can be supplied by any suitable source known in the art. Non-limiting sources of dietary butyrate includes animal source fats and derived products, such as but not limited to milk, milk fat, butter, buttermilk, butter serum, cream; microbial fermentation derived products, such as but not limited to yogurt and fermented buttermilk; and plant source derived seed oil products, such as pineapple and/or pineapple oil, apricot

and/or apricot oil, barley, oats, brown rice, bran, green beans, legumes, leafy greens, apples, kiwi, oranges. In some embodiments, the dietary butyrate is synthetically produced. In embodiments where the dietary butyrate is synthetically produced, the chemical structure of the dietary butyrate may be modified as necessary. Further, the dietary butyrate produced synthetically can be purified by any means known in the art to produce a purified dietary butyrate additive that can be incorporated into the nutritional compositions disclosed herein. The dietary butyrate may be provided by dairy lipids and/or triglyceride bound forms of butyrate.

[0052] In some embodiments, the dietary butyrate may be provided in an encapsulated form. In certain embodiments, the encapsulation of the dietary butyrate may provide for longer shelf-stability and may provide for improved organoleptic properties of the nutritional composition. For example, in some embodiments, the dietary butyrate may be encapsulated or coated by the use of, or combination of, fat derived materials, such as mono- and di-glycerides; sugar and acid esters of glycerides; phospholipids; plant, animal and microbial derived proteins and hydrocolloids, such as starches, maltodextrins, gelatin, pectins, glucans, caseins, soy proteins, and/or whey proteins.

[0053] The dietary butyric acid may also be provided in a coated form. For example, coating certain glycerol esters of butyric acids and/or amide derivatives of butyric acids with fat derived materials, such as mono- and di-glycerides; sugar and acid esters of glycerides; phospholipids; plant, animal and microbial derived proteins and hydrocolloids, such as starches, maltodextrins, gelatin, pectins, glucans, caseins, soy proteins, and/or whey proteins may improve the shelf-stability of the dietary butyrate and may further improve the overall organoleptic properties of the nutritional composition.

[0054] In certain embodiments, the dietary butyrate comprises glycerol esters of butyric acid. Glycerol esters of butyric acid may offer minimal complexity when formulated and processed in the nutritional composition. Additionally, glycerol esters of butyric acid may improve the shelf life of the nutritional composition including dietary butyrate an may further have a low impact on the sensory attributes of the finished product.

[0055] In some embodiments, the dietary butyrate may comprise butyrate salts, for example, sodium butyrate, potassium butyrate, calcium butyrate, magnesium butyrate, and combinations thereof. In some embodiments, the use of selected dietary butyrate salts may improve intestinal health when provided to target subjects. In certain embodiments, dietary butyrate comprises a suitable butyrate salt that has been coated with one or more fats or lipids. In certain embodiments wherein the dietary butyrate comprises a fat coated butyrate salt, the nutritional composition may be a dry-powdered composition into which the dietary butyrate is incorporated.

[0056] In some embodiments, the dietary butyrate may comprise any of the butyrate compounds disclosed herein that are formulated to be in complex form with chitosan or one or cyclodextrins. For example, cyclodextrins are cyclic oligosaccharides composed of six (α-cyclodextrin), seven (β-cyclodextrin), or eight (gamma-cyclodextrin) units of α-1,4-glucopyranose. Cyclodextrins are further characterized by a hydrophilic exterior surface and a hydrophobic core. Without being bound by any particular theory, the aliphatic butyrate chain would form a complex with the cyclodextrin core, thus increasing its molecular weight and, thus, reducing the volatility of the butyrate compound. Accordingly, the bioavailability of dietary butyrate may be improved when the dietary butyrate includes butyrate compounds in complex form with one or more cyclodextrins. Further, cyclodextrins are bulky hydrophobic molecules that are resistant to stomach acid as well as gastrointestinal enzymes, thus administration of the butyrate-cyclodextrin complex as described herein would promote absorption of the dietary butyrate in the small intestines.

[0057] In some embodiments the dietary butyrate is provided from an enriched lipid fraction derived from milk. For example, bovine milk fat has a butyric acid content that may be 20 times higher than the butyric acid content in human milk fat. Furthermore, among the short chain fatty acids ("SCFAs") present in human milk, *i.e.* fatty acids having a carbon chain length from 4 to 12, butyric acid (C4) is one of the most predominant in bovine milk. As such, bovine milk fat and/or enriched fractions of bovine milk fat may be included in a nutritional composition to provide dietary butyrate.

[0058] In embodiments where the dietary butyrate is provided by an enriched lipid fraction derived from milk the enriched lipid fraction derived from milk may be produced by any number of fractionation techniques. These techniques include but are not limited to melting point fractionation, organic solvent fractionation, super critical fluid fractionation, and any variants and combinations thereof.

[0059] Furthermore, mixtures that may be subjected to the fractionation procedures to produce the enriched lipid fraction include, but are not limited to, bovine whole milk, bovine cream, caprine milk, ovine milk, yak milk, and/or mixtures thereof. In a preferred embodiment the milk mixture used to create the enriched lipid fraction is bovine milk.

[0060] In addition to providing dietary butyrate, the enriched lipid fraction may comprise an one of the following ingredients: saturated fatty acids; trans-fatty acids; branched-chain fatty acids ("BCFAs"), including odd-branched chain fatty acids ("OBCFAs"); conjugated linoleic acid ("CLA"); monounsaturated fatty acids; polyunsaturated fatty acids; cholesterol; phospholipids; and milk fat globule membrane, including milk fat globule membrane protein.

[0061] In some embodiments the enriched lipid fraction includes, per 100 Kcal, one or more of the following:

from about 0.1 g to 8.0 g of saturated fatty acids;

from about 0.2 g to 7.0 g trans-fatty acids;

from about 0.003 g to about 6.1 g branched-chain fatty acids;

from about 0.026 g to about 2.5 g conjugated linoleic acid;

from about 0.8 g to about 2.5 g monounsaturated fatty acids;

from about 2.3 g to about 4.4 g polyunsaturated fatty acids;

from about 100 mg to about 400 mg of cholesterol;

from about 50 mg to about 400 mg of phospholipids; and/or

from about 10 mg to about 500 mg of milk fat globule membrane.

[0062] The following example illustrates a milk fat fraction having an enriched concentration of butyric acid (C4) that may be produced by a fractionation procedure.

Example 1

[0063] Illustrated below is a lipid profile of fractionated milk fat produced by super critical carbon extraction fractionation procedure and by melt-fractionation.

Milk Fat composition (g fatty acid /100 g TOTAL fatty acids)

	AMF	SCCO2	MeltFrac 10C
C 4:0	3.9	6.0	4.7
C 6:0	2.5	3.3	2.9
C 8:0	1.4	1.9	1.8
C 10:0	3.1	3.9	3.8
C 12:0	4.2	4.1	4.8
C 14:0	11.4	12.2	10.9
C 14:1	1.1	1.0	1.3
C 15:0	1.1	1.0	0.9
C 16:0	29.4	29.6	22.3
C 16:1	1.9	1.4	2.2
C 17:0	0.6	0.5	0.4
C 18:0	11.4	8.2	6.1
C 18:1, cis, ω9	21.9	16.5	25.3
C 18:1, trans, ω9	0.3	1.6	1.9
C 18:2, ω6	1.9	2.2	1.9
C 18:3, ω3, α	0.6	0.4	0.6
C 20:0	0.0	0.1	0.1

C 20:1, ω9	0.1	0.1	0.2
Saturated	68.7	70.7	58.6
Unsaturated	27.8	23.1	33.3

AMF = anhydrous milk fat; SCCO2 = super-critical carbon dioxide fraction (super olein). MeltFrac = melt crystallization fraction separated at 10°C.

[0064] In certain embodiments, the PDX- and GOS-containing prebiotic and dietary butyrate is incorporated into a nutritional composition that is an infant formula. Currently, many infant formulas are not formulated with dietary butyrate. One reason that infant formulas include little to no dietary butyrate is due to the unpleasant organoleptic properties exhibited by the nutritional composition when butyrate compounds are incorporated into the nutritional composition. For example, many butyrate compounds exhibit an odor that makes consuming the nutritional composition in which they are incorporated an unpleasant experience. Furthermore, the pediatric and infant population will not readily consume nutritional products having an unpleasant odor, taste, and/or mouthfeel. Accordingly, there exists a need for a nutritional composition formulated for administration to a pediatric subject or an infant that provides butyrate in the gut yet does not have diminished organoleptic properties. The incorporation of a prebiotic to stimulate butyrate production by gut microbiota and certain dietary butyrate compounds disclosed herein, *i.e.* glycerol esters of butyric acid and amide derivatives of amino acids, into pediatric and infant nutritional compositions will provide butyrate while still providing a pleasant sensory experience.

[0065] In some embodiments, the nutritional composition includes a protein equivalent source, wherein the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63. In some embodiments, the peptide component may comprise additional peptides disclosed in Table 1. For example, the composition may include at least 10 additional peptides disclosed in Table 1. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component, and 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, and combinations thereof. In some embodiments, the term additional means selecting different peptides than those enumerated.

[0066] In another embodiment 1% to 99% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID

NO 63, and at least 5 additional peptides selected from Table 1; and wherein 1% to 99% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof. In some embodiments 2% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 2% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof. In some embodiments 20% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof.

[0067] Table 1 below identifies the amino acid sequences of the peptides that may be included in the peptide component of the present nutritional compositions.

TABLE 1

Seq. ID Number	**Amino Acid Sequence**											**(aa)**
1	Ala	Ile	Asn	Pro	Ser	Lys	Glu	Asn				8
2	Ala	Pro	Phe	Pro	Glu							5
3	Asp	Ile	Gly	Ser	Glu	Ser						6
4	Asp	Lys	Thr	Glu	Ile	Pro	Thr					7
5	Asp	Met	Glu	Ser	Thr							5
6	Asp	Met	Pro	Ile								4
7	Asp	Val	Pro	Ser								4
n/a	Glu	Asp	Ile									3
n/a	Glu	Leu	Phe									3
n/a	Glu	Met	Pro									3
8	Glu	Thr	Ala	Pro	Val	Pro	Leu					7
9	Phe	Pro	Gly	Pro	Ile	Pro						6
10	Phe	Pro	Gly	Pro	Ile	Pro	Asn					7
11	Gly	Pro	Phe	Pro								4
12	Gly	Pro	Ile	Val								4

13	Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln			9
14	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser				8
15	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala			9
16	Ile	Asn	Pro	Ser	Lys	Glu						6
17	Ile	Pro	Asn	Pro	Ile							5
18	Ile	Pro	Asn	Pro	Ile	Gly						6
19	Ile	Pro	Pro	Leu	Thr	Gln	Thr	Pro	Val			9
20	Ile	Thr	Ala	Pro								4
21	Ile	Val	Pro	Asn								4
22	Lys	His	Gln	Gly	Leu	Pro	Gln					7
23	Leu	Asp	Val	Thr	Pro							5
24	Leu	Glu	Asp	Ser	Pro	Glu						6
25	Leu	Pro	Leu	Pro	Leu							5
26	Met	Glu	Ser	Thr	Glu	Val						6
27	Met	His	Gln	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr	11
28	Asn	Ala	Val	Pro	Ile							5
29	Asn	Glu	Val	Glu	Ala							5
n/a	Asn	Leu	Leu									3
30	Asn	Gln	Glu	Gln	Pro	Ile						6
31	Asn	Val	Pro	Gly	Glu							5
32	Pro	Phe	Pro	gly	Pro	Ile						6
33	Pro	Gly	Pro	Ile	Pro	Asn						6
34	Pro	His	Gln	Pro	Leu	Pro	Pro	Thr				8
35	Pro	Ile	Thr	Pro	Thr							5
36	Pro	Asn	Pro	Ile								4
37	Pro	Asn	Ser	Leu	Pro	Gln						6
38	Pro	Gln	Leu	Glu	Ile	Val	Pro	Asn				8
39	Pro	Gln	Asn	Ile	Pro	Pro	Leu					7
40	Pro	Val	Leu	Gly	Pro	Val						6
41	Pro	Val	Pro	Gln								4
42	Pro	Val	Val	Val	Pro							5
43	Pro	Val	Val	Val	Pro	Pro						6
44	Ser	Ile	Gly	Ser	Ser	Ser	Glu	Glu	Ser	Ala	Glu	11
45	Ser	Ile	Ser	Ser	Ser	Glu	Glu					7

46	Ser	Ile	Ser	Ser	Ser	Glu	Glu	Ile	Val	Pro	Asn	11
47	Ser	Lys	Asp	Ile	Gly	Ser	Glu					7
48	Ser	Pro	Pro	Glu	Ile	Asn						6
49	Ser	Pro	Pro	Glu	Ile	Asn	Thr					7
50	Thr	Asp	Ala	Pro	Ser	Phe	Ser					7
51	Thr	Glu	Asp	Glu	Leu							5
52	Val	Ala	Thr	Glu	Glu	Val						6
53	Val	Leu	Pro	Val	Pro							5
54	Val	Pro	Gly	Glu								4
55	Val	Pro	Gly	Glu	Ile	Val						6
56	Val	Pro	Ile	Thr	Pro	Thr						6
57	Val	Pro	Ser	Glu								4
58	Val	Val	Pro	Pro	Phe	Leu	Gln	Pro	Glu			9
59	Val	Val	Val	Pro	Pro							5
60	Tyr	Pro	Phe	Pro	Gly	Pro						6
61	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro				8
62	Tyr	Pro	Phe	Pro	Gly	Pro	Ile	Pro	Asn			9
63	Tyr	Pro	Ser	Gly	Ala							5
64	Tyr	Pro	Val	Glu	Pro							5

[0068] Table 2 below further identifies a subset of amino acid sequences from Table 1 that may be included in the peptide component disclosed herein.

TABLE 2

Seq ID Number		**Amino Acid Sequence**											**(aa)**
4		Asp	Lys	Thr	Glu	Ile	Pro	Thr					7
13		Ile	Gly	Ser	Glu	Ser	Thr	Glu	Asp	Gln			9
17		Ile	Pro	Asn	Pro	Ile	Gly						6
21		Ile	Val	Pro	Asn								4
24		Leu	Glu	Asp	Ser	Pro	Glu						6
30		Asn	Gln	Glu	Gln	Pro	Ile						6
31		Asn	Val	Pro	Gly	Glu							5
32		Pro	Phe	Pro	Gly	Pro	Ile						6
51		Thr	Glu	Asp	Glu	Leu							5
57		Val	Pro	Ser	Glu								4

60		Tyr	Pro	Phe	Pro	Gly	Pro						6
63		Tyr	Pro	Ser	Gly	Ala							5

[0069] In some embodiments, the peptide component may be present in the nutritional composition in an amount from about 0.2 g/100 Kcal to about 5.6 g/100 Kcal. In other embodiments the peptide component may be present in the nutritional composition in an amount from about 1 g/100 Kcal to about 4 g/100 Kcal. In still other embodiments, the peptide component may be present in the nutritional composition in an amount from about 2 g/100 Kcal to about 3 g/100 Kcal.

[0070] The peptide component disclosed herein may be formulated with other ingredients in the nutritional composition to provide appropriate nutrient levels for the target subject. In some embodiments, the peptide component is included in a nutritionally complete formula that is suitable to support normal growth.

[0071] The peptide component may be provided as an element of a protein equivalent source. In some embodiments, the peptides identified in Tables 1 and 2, may be provided by a protein equivalent source obtained from cow's milk proteins, including but not limited to bovine casein and bovine whey. In some embodiments, the protein equivalent source comprises hydrolyzed bovine casein or hydrolyzed bovine whey. Accordingly, in some embodiments, the peptides identified in Table 1 and Table 2 may be provided by a casein hydrolysate. Such peptides may be obtained by hydrolysis or may be synthesized in vitro by methods know to the skilled person.

[0072] A non-limiting example of a method of hydrolysis is disclosed herein. In some embodiments, this method may be used to obtain the protein hydrolysate and peptides of the present disclosure. The proteins are hydrolyzed using a proteolytic enzyme, Protease N. Protease N "Amano" is commercially available from Amano Enzyme U.S.A. Co., Ltd., Elgin, Ill. Protease N is a proteolytic enzyme preparation that is derived from the bacterial species Bacillus subtilis. The protease powder is specified as "not less than 150,000 units/g", meaning that one unit of Protease N is the amount of enzyme which produces an amino acid equivalent to 100 micrograms of tyrosine for 60 minutes at a pH of 7.0. To produce the infant formula of the present disclosure, Protease N can be used at levels of about 0.5% to about 1.0% by weight of the total protein being hydrolyzed.

[0073] The protein hydrolysis by Protease N is typically conducted at a temperature of about 50° C. to about 60° C. The hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis between about 4% and 10%. In a particular embodiment, hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis between about 6% and 9%. In another

embodiment, hydrolysis occurs for a period of time so as to obtain a degree of hydrolysis of about 7.5%. This level of hydrolysis may take between about one half hour to about 3 hours.

[0074] A constant pH should be maintained during hydrolysis. In the method of the present disclosure, the pH is adjusted to and maintained between about 6.5 and 8. In a particular embodiment, the pH is maintained at about 7.0.

[0075] In order to maintain the optimal pH of the solution of whey protein, casein, water and Protease N, a caustic solution of sodium hydroxide and/or potassium hydroxide can be used to adjust the pH during hydrolysis. If sodium hydroxide is used to adjust the pH, the amount of sodium hydroxide added to the solution should be controlled to the level that it comprises less than about 0.3% of the total solid in the finished protein hydrolysate. A 10% potassium hydroxide solution can also be used to adjust the pH of the solution to the desired value, either before the enzyme is added or during the hydrolysis process in order to maintain the optimal pH.

[0076] The amount of caustic solution added to the solution during the protein hydrolysis can be controlled by a pH-stat or by adding the caustic solution continuously and proportionally. The hydrolysate can be manufactured by standard batch processes or by continuous processes.

[0077] To better ensure the consistent quality of the protein partial hydrolysate, the hydrolysate is subjected to enzyme deactivation to end the hydrolysis process. The enzyme deactivation step may consist include at heat treatment at a temperature of about 82° C. for about 10 minutes. Alternatively, the enzyme can be deactivated by heating the solution to a temperature of about 92° C. for about 5 seconds. After enzyme deactivation is complete, the hydrolysate can be stored in a liquid state at a temperature lower than 10° C.

[0078] In some embodiments, the protein equivalent source comprises a hydrolyzed protein, which includes partially hydrolyzed protein and extensively hydrolyzed protein, such as casein. In some embodiments, the protein equivalent source comprises a hydrolyzed protein including peptides having a molar mass distribution of greater than 500 Daltons. In some embodiments, the hydrolyzed protein comprises peptides having a molar mass distribution in the range of from about 500 Daltons to about 1,500 Daltons. Still, in some embodiments the hydrolyzed protein may comprise peptides having a molar mass distribution range of from about 500 Daltons to about 2,000 Daltons.

[0079] In some embodiments, the protein equivalent source may comprise the peptide component, intact protein, hydrolyzed protein, including partially hydrolyzed protein and/or extensively hydrolyzed protein, and combinations thereof. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component disclosed herein. In some embodiments, 30% to 60% of the protein equivalent source comprises the peptide

component disclosed herein. In still other embodiments, 40% to 50% of the protein equivalent source comprises the peptide component.

[0080] In some embodiments, 20% to 80% of the protein equivalent source comprises intact protein, partially hydrolyzed protein, extensively hydrolyzed protein, or combinations thereof. In some embodiments, 40% to 70% of the protein equivalent source comprises intact proteins, partially hydrolyzed proteins, extensively hydrolyzed protein, or a combination thereof. In still further embodiments, 50% to 60% of the protein equivalent source may comprise intact proteins, partially hydrolyzed protein, extensively hydrolyzed protein, or a combination thereof.

[0081] In some embodiments the protein equivalent source comprises partially hydrolyzed protein having a degree of hydrolysis of less than 40%. In still other embodiments, the protein equivalent source may comprise partially hydrolyzed protein having a degree of hydrolysis of less than 25%, or less than 15%.

[0082] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein equivalent source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein equivalent source per 100 Kcal.

[0083] Without being bound by any particular theory, the administration of a nutritional composition as disclosed herein may reduce allergic response and may improve tolerance to cow's milk allergy in certain subjects. In some embodiments, the combination of prebiotic, dietary butyrate, and the protein equivalent source provide synergistic health benefits.

[0084] The nutritional composition may be protein-free in some embodiments and comprise free amino acids as an element of the protein equivalent source. In some embodiments, the amino acids may be branched chain amino acids. In certain other embodiments, small amino acid peptides may be included as the protein component of the nutritional composition. Such small amino acid peptides may be naturally occurring or synthesized. In some embodiments, the amount of free amino acids in the nutritional composition may vary from about 1 g/100 Kcal to about 5 g/100 Kcal.

[0085] In certain embodiments, the protein equivalent source comprises amino acids and is substantially free of whole, intact protein. Further in certain embodiments, the protein equivalent source comprises amino acids and is substantially free of peptides. In certain embodiments, the protein equivalent source includes from about 10% to about 90% w/w of essential amino acids based on the total amino acids included in the protein equivalent source. In certain embodiments, the protein equivalent source includes from about 25% to about 75% w/w of essential amino acids based on the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes

from about 40% to about 60% of essential amino acids based on the total amino acids included in the protein equivalent source.

[0086] In some embodiments, the protein equivalent source includes non-essential amino acids. In certain embodiments, the protein equivalent source includes from about 10% to about 90% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source. In certain embodiments, the protein equivalent source includes from about 25% to about 75% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 40% to about 60% w/w of non-essential amino acids based on the total amino acids included in the protein equivalent source.

[0087] In some embodiments, the protein equivalent source includes leucine. In some embodiments, the protein equivalent source includes from about 2% to about 15% w/w leucine per the total amount of amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 10% w/w leucine per the total amount of amino acids included in the protein equivalent source.

[0088] In some embodiments, the protein equivalent source includes lysine. In some embodiments, the protein equivalent source includes from about 2% to about 10% w/w lysine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 8% w/w lysine per the total amino acids in the protein equivalent source.

[0089] In some embodiments, the protein equivalent source includes valine. In some embodiments, the protein equivalent source includes from about 2% to about 15% w/w valine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 4% to about 10% w/w valine per the total amino acids in the protein equivalent source.

[0090] In some embodiments, the protein equivalent source includes isoleucine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w isoleucine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w isoleucine per the total amino acids in the protein equivalent source.

[0091] In some embodiments, the protein equivalent source includes threonine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w threonine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w threonine per the total amino acids in the protein equivalent source.

[0092] In some embodiments, the protein equivalent source includes tyrosine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w tyrosine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w tyrosine per the total amino acids in the protein equivalent source.

[0093] In some embodiments, the protein equivalent source includes phenylalanine. In some embodiments, the protein equivalent source includes from about 1% to about 8% w/w phenylalanine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 7% w/w phenylalanine per the total amino acids in the protein equivalent source.

[0094] In some embodiments, the protein equivalent source includes histidine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w histidine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w histidine per the total amino acids in the protein equivalent source.

[0095] In some embodiments, the protein equivalent source includes cystine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w cystine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w cystine per the total amino acids in the protein equivalent source.

[0096] In some embodiments, the protein equivalent source includes tryptophan. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w tryptophan per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w tryptophan per the total amino acids in the protein equivalent source.

[0097] In some embodiments, the protein equivalent source includes methionine. In some embodiments, the protein equivalent source includes from about 0.5% to about 4% w/w methionine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w methionine per the total amino acids in the protein equivalent source.

[0098] In some embodiments, the protein equivalent source includes aspartic acid. In some embodiments, the protein equivalent source includes from about 7% to about 20% w/w aspartic acid per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 10% to about 17% w/w aspartic acid per the total amino acids in the protein equivalent source.

[0099] In some embodiments, the protein equivalent source includes proline. In some embodiments, the protein equivalent source includes from about 5% to about 12% w/w proline per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 7% to about 10% w/w proline per the total amino acids in the protein equivalent source.

[0100] In some embodiments, the protein equivalent source includes alanine. In some embodiments, the protein equivalent source includes from about 3% to about 10% w/w alanine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 5% to about 8% w/w alanine per the total amino acids in the protein equivalent source.

[0101] In some embodiments, the protein equivalent source includes glutamate. In some embodiments, the protein equivalent source includes from about 1.5% to about 8% w/w glutamate per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 6% w/w glutamate per the total amino acids in the protein equivalent source.

[0102] In some embodiments, the protein equivalent source includes serine. In some embodiments, the protein equivalent source includes from about 1.5% to about 8% w/w serine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3% to about 5% w/w serine per the total amino acids in the protein equivalent source.

[0103] In some embodiments, the protein equivalent source includes arginine. In some embodiments, the protein equivalent source includes from about 2% to about 8% w/w arginine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 3.5% to about 6% w/w arginine per the total amino acids in the protein equivalent source.

[0104] In some embodiments, the protein equivalent source includes glycine. In some embodiments, the protein equivalent source includes from about 0.5% to about 6% w/w glycine per the total amino acids included in the protein equivalent source. In some embodiments, the protein equivalent source includes from about 1.5% to about 3.5% w/w glycine per the total amino acids in the protein equivalent source.

[0105] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein equivalent source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein equivalent source per 100 Kcal.

[0106] In some embodiments, the nutritional composition comprises between about 0.5 g/100 Kcal and about 2.5 g/100 Kcal of essential amino acids. In certain embodiments, the

nutritional composition comprises between about 1.3 g/100 Kcal to about 1.6 Kcal of essential amino acids.

[0107] In some embodiments, the nutritional composition comprises between about 0.5 g/100 Kcal and about 2.5 g/100 Kcal of essential amino acids. In certain embodiments, the nutritional composition comprises between about 1.3 g/100 Kcal to about 1.6 Kcal of non-essential amino acids.

[0108] In some embodiments, the nutritional composition comprises from about 0.2 g/100 Kcal to about 0.5 g/100 Kcal of leucine. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of lysine. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of valine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.23 g/100 Kcal of isoleucine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.20 g/100 Kcal of threonine. In some embodiments, the nutritional composition comprises from about 0.10 g/100 Kcal to about 0.15 g/100 Kcal of tyrosine. In some embodiments, the nutritional composition comprises from about 0.05 g/100 Kcal to about 0.15 g/100 Kcal of phenylalanine. In some embodiments, the nutritional composition comprises from about 0.01 g/100 Kcal to about 0.09 g/100 Kcal of histidine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of cystine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of tryptophan. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of methionine.

[0109] In some embodiments, the nutritional composition comprises from about 0.2 g/100 Kcal to about 0.7 g/100 Kcal of aspartic acid. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.4 g/100 Kcal of proline. In some embodiments, the nutritional composition comprises from about 0.1 g/100 Kcal to about 0.3 g/100 Kcal of alanine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.25 g/100 Kcal of glutamate. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.2 g/100 Kcal of serine. In some embodiments, the nutritional composition comprises from about 0.08 g/100 Kcal to about 0.15 g/100 Kcal of arginine. In some embodiments, the nutritional composition comprises from about 0.02 g/100 Kcal to about 0.08 g/100 Kcal of glycine.

[0110] The nutritional composition(s) of the present disclosure including the protein equivalent source, may be administered in one or more doses daily. Any orally acceptable dosage form is contemplated by the present disclosure. Examples of such dosage forms include, but are not limited to pills, tablets, capsules, soft-gels, liquids, liquid concentrates,

powders, elixirs, solutions, suspensions, emulsions, lozenges, beads, cachets, and combinations thereof.

[0111] In some embodiments, the protein equivalent source may provide from about 5% to about 20% of the total calories for the nutritional composition. In some embodiments, the protein equivalent source may provide from about 8% to about 12 % of the total calories for the nutritional composition.

[0112] In some embodiments, without being bound by any particular theory, the nutritional compositions including dietary butyrate, prebiotic, and the protein equivalent source disclosed herein, may reduce the incidence of allergic reactions in human subjects when administered. For example, in certain embodiments the nutritional compositions may include dietary butyrate, prebiotic, and a protein equivalent source, where the protein equivalent source is substantially free of whole and/or intact protein. As such, the protein equivalent source provides amino acids in addition to dietary butyrate, which, in combination, may further prevent allergic reaction and decrease inflammation when administered.

[0113] The nutritional composition(s) of the present disclosure may also comprise a carbohydrate source. Carbohydrate sources can be any used in the art, e.g., lactose, glucose, fructose, corn syrup solids, maltodextrins, sucrose, starch, rice syrup solids, and the like. The amount of carbohydrate in the nutritional composition typically can vary from between about 5 g and about 25 g/100 Kcal. In some embodiments, the amount of carbohydrate is between about 6 g and about 22 g/ 100 Kcal. In other embodiments, the amount of carbohydrate is between about 12 g and about 14 g/100 Kcal. In some embodiments, corn syrup solids are preferred. Moreover, hydrolyzed, partially hydrolyzed, and/or extensively hydrolyzed carbohydrates may be desirable for inclusion in the nutritional composition due to their easy digestibility. Specifically, hydrolyzed carbohydrates are less likely to contain allergenic epitopes.

[0114] Non-limiting examples of carbohydrate materials suitable for use herein include hydrolyzed or intact, naturally or chemically modified, starches sourced from corn, tapioca, rice or potato, in waxy or non-waxy forms. Non-limiting examples of suitable carbohydrates include various hydrolyzed starches characterized as hydrolyzed cornstarch, maltodextrin, maltose, corn syrup, dextrose, corn syrup solids, glucose, and various other glucose polymers and combinations thereof. Non-limiting examples of other suitable carbohydrates include those often referred to as sucrose, lactose, fructose, high fructose corn syrup, indigestible oligosaccharides such as fructooligosaccharides and combinations thereof.

[0115] The nutritional composition(s) of the disclosure may also comprise a protein source. The protein source can be any used in the art, e.g., nonfat milk, whey protein, casein, soy protein, hydrolyzed protein, amino acids, and the like. Bovine milk protein sources useful in

practicing the present disclosure include, but are not limited to, milk protein powders, milk protein concentrates, milk protein isolates, nonfat milk solids, nonfat milk, nonfat dry milk, whey protein, whey protein isolates, whey protein concentrates, sweet whey, acid whey, casein, acid casein, caseinate (*e.g.* sodium caseinate, sodium calcium caseinate, calcium caseinate) and any combinations thereof.

[0116] In one embodiment, the proteins of the nutritional composition are provided as intact proteins. In other embodiments, the proteins are provided as a combination of both intact proteins and partially hydrolyzed proteins, with a degree of hydrolysis of between about 4% and 10%. In certain other embodiments, the proteins are more completely hydrolyzed. In still other embodiments, the protein source comprises amino acids. In yet another embodiment, the protein source may be supplemented with glutamine-containing peptides.

[0117] In a particular embodiment of the nutritional composition, the whey:casein ratio of the protein source is similar to that found in human breast milk. In an embodiment, the protein source comprises from about 40% to about 80% whey protein and from about 20% to about 60% casein.

[0118] In some embodiments, the nutritional composition comprises between about 1 g and about 7 g of a protein source per 100 Kcal. In other embodiments, the nutritional composition comprises between about 3.5 g and about 4.5 g of protein per 100 Kcal.

[0119] In some embodiments, the nutritional composition described herein comprises a fat source. The enriched lipid fraction described herein may be the sole fat source or may be used in combination with any other suitable fat or lipid source for the nutritional composition as known in the art. In certain embodiments, appropriate fat sources include, but are not limited to, animal sources, e.g., milk fat, butter, butter fat, egg yolk lipid; marine sources, such as fish oils, marine oils, single cell oils; vegetable and plant oils, such as corn oil, canola oil, sunflower oil, soybean oil, palm olein oil, coconut oil, high oleic sunflower oil, evening primrose oil, rapeseed oil, olive oil, flaxseed (linseed) oil, cottonseed oil, high oleic safflower oil, palm stearin, palm kernel oil, wheat germ oil; medium chain triglyceride oils and emulsions and esters of fatty acids; and any combinations thereof.

[0120] In some embodiment the nutritional composition comprises between about 1 g/100 Kcal to about 10 g/100 Kcal of a fat or lipid source. In some embodiments, the nutritional composition comprises between about 2 g/100 Kcal to about 7 g/100 Kcal of a fat source. In other embodiments the fat source may be present in an amount from about 2.5 g/100 Kcal to about 6 g/100 Kcal. In still other embodiments, the fat source may be present in the nutritional composition in an amount from about 3 g/100 Kcal to about 4 g/100 Kcal.

[0121] In some embodiments, the fat or lipid source comprises from about 10% to about 35% palm oil per the total amount of fat or lipid. In some embodiments, the fat or lipid

source comprises from about 15% to about 30% palm oil per the total amount of fat or lipid. Yet in other embodiments, the fat or lipid source may comprise from about 18% to about 25 % palm oil per the total amount of fat or lipid.

[0122] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% soybean oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% soybean oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% soybean oil based on the total amount of fat or lipid.

[0123] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% coconut oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% coconut oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% coconut oil based on the total amount of fat or lipid.

[0124] In certain embodiments, the fat or lipid source may be formulated to include from about 2% to about 16% sunflower oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 4% to about 12% sunflower oil based on the total amount of fat or lipid. In some embodiments, the fat or lipid source may be formulated to include from about 6% to about 10% sunflower oil based on the total amount of fat or lipid.

[0125] In some embodiments, the oils, *i.e.* sunflower oil, soybean oil, sunflower oil, palm oil, etc. are meant to cover fortified versions of such oils known in the art. For example, in certain embodiments, the use of sunflower oil may include high oleic sunflower oil. In other examples, the use of such oils may be fortified with certain fatty acids, as known in the art, and may be used in the fat or lipid source disclosed herein.

[0126] In some embodiments, the fat or lipid source includes an oil blend including sunflower oil, medium chain triglyceride oil, and soybean oil. In some embodiments, the fat or lipid source includes a ratio of sunflower oil to medium chain triglyceride oil of about 1:1 to about 2:1. In certain other embodiments, the fat or lipid source includes a ratio of sunflower oil to soybean oil of from about 1:1 to about 2:1. In still other embodiments, the fat or lipid source may include a ratio of medium chain triglyceride oil to soybean oil of from about 1:1 to about 2:1.

[0127] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w sunflower oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w sunflower oil based on the total

fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w sunflower oil based on the total fat or lipid content.

[0128] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w medium chain triglyceride oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w medium chain triglyceride oil based on the total fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w medium chain triglyceride oil based on the total fat or lipid content.

[0129] In certain embodiments the fat or lipid source may comprise from about 15% to about 50% w/w soybean oil based on the total fat or lipid content. In certain embodiments, the fat or lipid source includes from about 25% to about 40% w/w soybean oil based on the total fat or lipid content. In some embodiments, the fat or lipid source comprises from about 30% to about 35% w/w soybean oil based on the total fat or lipid content.

[0130] In some embodiments, the nutritional composition comprises from about 1 g/100 Kcal to about 3 g/100 Kcal of sunflower oil. In some embodiments, the nutritional composition comprises from about 1.3 g/100 Kcal to about 2.5 g/100 Kcal of sunflower oil. In still other embodiments, the nutritional composition comprises from about 1.7 g/100 Kcal to about 2.1 g/100 Kcal of sunflower oil. The sunflower oil as described herein may, in some embodiments, include high oleic sunflower oil.

[0131] In certain embodiments, the nutritional composition if formulated to include from about 1 g/100 Kcal to about 2.5 g/100 Kcal of medium chain triglyceride oil. In other embodiments, the nutritional composition includes from about 1.3 g/100 Kcal to about 2.1 g/100 Kcal of medium chain triglyceride oil. Still in further embodiments, the nutritional composition includes from about 1.6 g/100 Kcal to about 1.9 g/100 Kcal of medium chain triglyceride oil.

[0132] In some embodiments, the nutritional composition may be formulated to include from about 1 g/100 Kcal to about 2.3 g/100 Kcal of soybean oil. In certain embodiments, the nutritional composition may be formulated to include from about 1.2 g/100 Kcal to about 2 g/100 Kcal of soybean oil. Still in certain embodiments, the nutritional composition may be formulated to include from about 1.5 g/100 Kcal to about 1.8 g/100 Kcal of soybean oil.

[0133] In some embodiments, the term "sunflower oil", "medium chain triglyceride oil", and "soybean oil" are meant to cover fortified versions of such oils known in the art. For example, in certain embodiments, the use of sunflower oil may include high oleic sunflower oil. In other examples, the use of such oils may be fortified with certain fatty acids, as known in the art, and may be used in the fat or lipid source disclosed herein.

[0134] In some embodiments, the fat or lipid source provides from about 35% to about 55% of the total calories of the nutritional composition. In other embodiments, the fat or lipid source provides from about 40% to about 47% of the total calories of the nutritional composition.

[0135] In certain embodiments the nutritional composition may be formulated, in some embodiments, such that from about 10% to about 23 % of the total calories of the nutritional composition are provided by sunflower oil. In other embodiments, from about 13% to about 20% of the total calories in the nutritional composition may be provided by sunflower oil. Still, in other embodiments, from about 15 % to about 18% of the total calories of the nutritional composition may be provided by sunflower oil.

[0136] In some embodiments, the nutritional composition may be formulated such that from about 10% to about 20% of the total calories are provided by MCT oil. In certain embodiments, from about 12% to about 18% of the total calories in the nutritional composition may be provided by MCT oil. Still , in certain embodiments, from about 14% to about 17% of the calories of the nutritional composition may be provided by MCT oil.

[0137] In some embodiments, the nutritional composition may be formulated such that from about 10% to 20% of the total calories of the nutritional composition are provided by soybean oil. In certain embodiments, from about 12% to about 18% of the total calories of the nutritional composition may be provided by soybean oil. In certain embodiments, from about 13% to about 16% of the total calories may be provided by soybean oil.

[0138] In some embodiments the nutritional composition may also include a source of LCPUFAs. In one embodiment the amount of LCPUFA in the nutritional composition is advantageously at least about 5 mg/100 Kcal, and may vary from about 5 mg/100 Kcal to about 100 mg/100 Kcal, more preferably from about 10 mg/100 Kcal to about 50 mg/100 Kcal. Non-limiting examples of LCPUFAs include, but are not limited to, DHA, ARA, linoleic (18:2 n-6), γ-linolenic (18:3 n-6), dihomo- γ-linolenic (20:3 n-6) acids in the n-6 pathway, α-linolenic (18:3 n-3), stearidonic (18:4 n-3), eicosatetraenoic (20:4 n-3), eicosapentaenoic (20:5 n-3), and docosapentaenoic (22:6 n-3).

[0139] In some embodiments, the LCPUFA included in the nutritional composition may comprise DHA. In one embodiment the amount of DHA in the nutritional composition is advantageously at least about 17 mg/100 Kcal, and may vary from about 5 mg/100 Kcal to about 75 mg/100 Kcal, more preferably from about 10 mg/100 Kcal to about 50 mg/100 Kcal.

[0140] In another embodiment, especially if the nutritional composition is an infant formula, the nutritional composition is supplemented with both DHA and ARA. In this embodiment,

the weight ratio of ARA:DHA may be between about 1:3 and about 9:1. In a particular embodiment, the ratio of ARA:DHA is from about 1:2 to about 4:1.

[0141] The DHA and ARA can be in natural form, provided that the remainder of the LCPUFA source does not result in any substantial deleterious effect on the infant. Alternatively, the DHA and ARA can be used in refined form.

[0142] The disclosed nutritional composition described herein can, in some embodiments, also comprise a source of ß-glucan. Glucans are polysaccharides, specifically polymers of glucose, which are naturally occurring and may be found in cell walls of bacteria, yeast, fungi, and plants. Beta glucans (β-glucans) are themselves a diverse subset of glucose polymers, which are made up of chains of glucose monomers linked together via beta-type glycosidic bonds to form complex carbohydrates.

[0143] β-1,3-glucans are carbohydrate polymers purified from, for example, yeast, mushroom, bacteria, algae, or cereals. (Stone BA, Clarke AE. Chemistry and Biology of (1-3)-Beta-Glucans. London:Portland Press Ltd; 1993.) The chemical structure of β-1,3-glucan depends on the source of the β-1,3-glucan. Moreover, various physiochemical parameters, such as solubility, primary structure, molecular weight, and branching, play a role in biological activities of β-1,3-glucans. (Yadomae T., *Structure and biological activities of fungal beta-1,3-glucans.* Yakugaku Zasshi. 2000;120:413-431.)

[0144] β-1,3-glucans are naturally occurring polysaccharides, with or without β-1,6-glucose side chains that are found in the cell walls of a variety of plants, yeasts, fungi and bacteria. β-1,3;1,6-glucans are those containing glucose units with (1,3) links having side chains attached at the (1,6) position(s). β-1,3;1,6 glucans are a heterogeneous group of glucose polymers that share structural commonalities, including a backbone of straight chain glucose units linked by a β-1,3 bond with β-1,6-linked glucose branches extending from this backbone. While this is the basic structure for the presently described class of β-glucans, some variations may exist. For example, certain yeast β-glucans have additional regions of β(1,3) branching extending from the β(1,6) branches, which add further complexity to their respective structures.

[0145] β-glucans derived from baker's yeast, *Saccharomyces cerevisiae*, are made up of chains of D-glucose molecules connected at the 1 and 3 positions, having side chains of glucose attached at the 1 and 6 positions. Yeast-derived β-glucan is an insoluble, fiber-like, complex sugar having the general structure of a linear chain of glucose units with a β-1,3 backbone interspersed with β-1,6 side chains that are generally 6-8 glucose units in length. More specifically, β-glucan derived from baker's yeast is poly-(1,6)-β-D-glucopyranosyl-(1,3)-β-D-glucopyranose.

[0146] Furthermore, β-glucans are well tolerated and do not produce or cause excess gas, abdominal distension, bloating or diarrhea in pediatric subjects. Addition of β-glucan to a nutritional composition for a pediatric subject, such as an infant formula, a growing-up milk or another children's nutritional product, will improve the subject's immune response by increasing resistance against invading pathogens and therefore maintaining or improving overall health.

[0147] In some embodiments, the β-glucan is β-1,3;1,6-glucan. In some embodiments, the β-1,3;1,6-glucan is derived from baker's yeast. The nutritional composition may comprise whole glucan particle β-glucan, particulate β-glucan, PGG-glucan (poly-1,6-β-D-glucopyranosyl-1,3-β-D-glucopyranose) or any mixture thereof.

[0148] In some embodiments, the amount of β-glucan in the nutritional composition is between about 3 mg and about 17 mg per 100 Kcal. In another embodiment the amount of β-glucan is between about 6 mg and about 17 mg per 100 Kcal.

[0149] The disclosed nutritional composition described herein can, in some embodiments, also comprise a source of probiotic. The term "probiotic" means a microorganism that exerts beneficial effects on the health of the host. Any probiotic known in the art may be acceptable in this embodiment. In a particular embodiment, the probiotic may be selected from any *Lactobacillus* species, *Lactobacillus rhamnosus* GG (ATCC number 53103), *Bifidobacterium* species, *Bifidobacterium longum* BB536 (BL999, ATCC: BAA-999), *Bifidobacterium longum* AH1206 (NCIMB: 41382), *Bifidobacterium breve* AH1205 (NCIMB: 41387), *Bifidobacterium infantis* 35624 (NCIMB: 41003), and *Bifidobacterium animalis subsp. lactis* BB-12 (DSM No. 10140) or any combination thereof.

[0150] If included, the nutritional composition may comprise between about 1×10^4 to about 1.5×10^{10} cfu of probiotics per 100 Kcal, more preferably from about 1×10^6 to about 1×10^9 cfu of probiotics per 100 Kcal.

[0151] In an embodiment, the probiotic(s) may be viable or non-viable. As used herein, the term "viable", refers to live microorganisms. The term "non-viable" or "non-viable probiotic" means non-living probiotic microorganisms, their cellular components and/or metabolites thereof. Such non-viable probiotics may have been heat-killed or otherwise inactivated, but they retain the ability to favorably influence the health of the host. The probiotics useful in the present disclosure may be naturally-occurring, synthetic or developed through the genetic manipulation of organisms, whether such new source is now known or later developed.

[0152] The disclosed nutritional composition described herein, can, in some embodiments also comprise an effective amount of iron. The iron may comprise encapsulated iron forms,

such as encapsulated ferrous fumarate or encapsulated ferrous sulfate or less reactive iron forms, such as ferric pyrophosphate or ferric orthophosphate.

[0153] One or more vitamins and/or minerals may also be added in to the nutritional composition in amounts sufficient to supply the daily nutritional requirements of a subject. It is to be understood by one of ordinary skill in the art that vitamin and mineral requirements will vary, for example, based on the age of the child. For instance, an infant may have different vitamin and mineral requirements than a child between the ages of one and thirteen years. Thus, the embodiments are not intended to limit the nutritional composition to a particular age group but, rather, to provide a range of acceptable vitamin and mineral components.

[0154] In embodiments providing a nutritional composition for a child, the composition may optionally include, but is not limited to, one or more of the following vitamins or derivations thereof: vitamin B_1 (thiamin, thiamin pyrophosphate, TPP, thiamin triphosphate, TTP, thiamin hydrochloride, thiamin mononitrate), vitamin B_2 (riboflavin, flavin mononucleotide, FMN, flavin adenine dinucleotide, FAD, lactoflavin, ovoflavin), vitamin B_3 (niacin, nicotinic acid, nicotinamide, niacinamide, nicotinamide adenine dinucleotide, NAD, nicotinic acid mononucleotide, NicMN, pyridine-3-carboxylic acid), vitamin B_3-precursor tryptophan, vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine, pyridoxine hydrochloride), pantothenic acid (pantothenate, panthenol), folate (folic acid, folacin, pteroylglutamic acid), vitamin B_{12} (cobalamin, methylcobalamin, deoxyadenosylcobalamin, cyanocobalamin, hydroxycobalamin, adenosylcobalamin), biotin, vitamin C (ascorbic acid), vitamin A (retinol, retinyl acetate, retinyl palmitate, retinyl esters with other long-chain fatty acids, retinal, retinoic acid, retinol esters), vitamin D (calciferol, cholecalciferol, vitamin D_3, 1,25,-dihydroxyvitamin D), vitamin E (α-tocopherol, α-tocopherol acetate, α-tocopherol succinate, α-tocopherol nicotinate, α-tocopherol), vitamin K (vitamin K_1, phylloquinone, naphthoquinone, vitamin K_2, menaquinone-7, vitamin K_3, menaquinone-4, menadione, menaquinone-8, menaquinone-8H, menaquinone-9, menaquinone-9H, menaquinone-10, menaquinone-11, menaquinone-12, menaquinone-13), choline, inositol, β-carotene and any combinations thereof.

[0155] In embodiments providing a children's nutritional product, such as a growing-up milk, the composition may optionally include, but is not limited to, one or more of the following minerals or derivations thereof: boron, calcium, calcium acetate, calcium gluconate, calcium chloride, calcium lactate, calcium phosphate, calcium sulfate, chloride, chromium, chromium chloride, chromium picolonate, copper, copper sulfate, copper gluconate, cupric sulfate, fluoride, iron, carbonyl iron, ferric iron, ferrous fumarate, ferric orthophosphate, iron trituration, polysaccharide iron, iodide, iodine, magnesium, magnesium carbonate, magnesium hydroxide, magnesium oxide, magnesium stearate, magnesium sulfate,

manganese, molybdenum, phosphorus, potassium, potassium phosphate, potassium iodide, potassium chloride, potassium acetate, selenium, sulfur, sodium, docusate sodium, sodium chloride, sodium selenate, sodium molybdate, zinc, zinc oxide, zinc sulfate and mixtures thereof. Non-limiting exemplary derivatives of mineral compounds include salts, alkaline salts, esters and chelates of any mineral compound.

[0156] The minerals can be added to growing-up milks or to other children's nutritional compositions in the form of salts such as calcium phosphate, calcium glycerol phosphate, sodium citrate, potassium chloride, potassium phosphate, magnesium phosphate, ferrous sulfate, zinc sulfate, cupric sulfate, manganese sulfate, and sodium selenite. Additional vitamins and minerals can be added as known within the art.

[0157] The nutritional compositions of the present disclosure may optionally include one or more of the following flavoring agents, including, but not limited to, flavored extracts, volatile oils, cocoa or chocolate flavorings, peanut butter flavoring, cookie crumbs, vanilla or any commercially available flavoring. Examples of useful flavorings include, but are not limited to, pure anise extract, imitation banana extract, imitation cherry extract, chocolate extract, pure lemon extract, pure orange extract, pure peppermint extract, honey, imitation pineapple extract, imitation rum extract, imitation strawberry extract, or vanilla extract; or volatile oils, such as balm oil, bay oil, bergamot oil, cedarwood oil, cherry oil, cinnamon oil, clove oil, or peppermint oil; peanut butter, chocolate flavoring, vanilla cookie crumb, butterscotch, toffee, and mixtures thereof. The amounts of flavoring agent can vary greatly depending upon the flavoring agent used. The type and amount of flavoring agent can be selected as is known in the art.

[0158] The nutritional compositions of the present disclosure may optionally include one or more emulsifiers that may be added for stability of the final product. Examples of suitable emulsifiers include, but are not limited to, lecithin (*e.g.*, from egg or soy), alpha lactalbumin and/or mono- and di-glycerides, and mixtures thereof. Other emulsifiers are readily apparent to the skilled artisan and selection of suitable emulsifier(s) will depend, in part, upon the formulation and final product.

[0159] The nutritional compositions of the present disclosure may optionally include one or more preservatives that may also be added to extend product shelf life. Suitable preservatives include, but are not limited to, potassium sorbate, sodium sorbate, potassium benzoate, sodium benzoate, calcium disodium EDTA, and mixtures thereof.

[0160] The nutritional compositions of the present disclosure may optionally include one or more stabilizers. Suitable stabilizers for use in practicing the nutritional composition of the present disclosure include, but are not limited to, gum arabic, gum ghatti, gum karaya, gum tragacanth, agar, furcellaran, guar gum, gellan gum, locust bean gum, pectin, low methoxyl

pectin, gelatin, microcrystalline cellulose, CMC (sodium carboxymethylcellulose), methylcellulose hydroxypropyl methyl cellulose, hydroxypropyl cellulose, DATEM (diacetyl tartaric acid esters of mono- and diglycerides), dextran, carrageenans, and mixtures thereof.

[0161] The nutritional compositions of the disclosure may provide minimal, partial or total nutritional support. The compositions may be nutritional supplements or meal replacements. The compositions may, but need not, be nutritionally complete. In an embodiment, the nutritional composition of the disclosure is nutritionally complete and contains suitable types and amounts of lipid, carbohydrate, protein, vitamins and minerals. The amount of lipid or fat typically can vary from about 1 to about 25 g/100 Kcal. The amount of protein typically can vary from about 1 to about 7 g/100 Kcal. The amount of carbohydrate typically can vary from about 6 to about 22 g/100 Kcal.

[0162] In an embodiment, the children's nutritional composition may contain between about 10 and about 50% of the maximum dietary recommendation for any given country, or between about 10 and about 50% of the average dietary recommendation for a group of countries, per serving of vitamins A, C, and E, zinc, iron, iodine, selenium, and choline. In another embodiment, the children's nutritional composition may supply about 10 – 30% of the maximum dietary recommendation for any given country, or about 10 – 30% of the average dietary recommendation for a group of countries, per serving of B-vitamins. In yet another embodiment, the levels of vitamin D, calcium, magnesium, phosphorus, and potassium in the children's nutritional product may correspond with the average levels found in milk. In other embodiments, other nutrients in the children's nutritional composition may be present at about 20% of the maximum dietary recommendation for any given country, or about 20% of the average dietary recommendation for a group of countries, per serving.

[0163] In some embodiments the nutritional composition is an infant formula. Infant formulas are fortified nutritional compositions for an infant. The content of an infant formula is dictated by federal regulations, which define macronutrient, vitamin, mineral, and other ingredient levels in an effort to simulate the nutritional and other properties of human breast milk. Infant formulas are designed to support overall health and development in a pediatric human subject, such as an infant or a child.

[0164] In some embodiments, the nutritional composition of the present disclosure is a growing-up milk. Growing-up milks are fortified milk-based beverages intended for children over 1 year of age (typically from 1-3 years of age, from 4-6 years of age or from 1-6 years of age). They are not medical foods and are not intended as a meal replacement or a supplement to address a particular nutritional deficiency. Instead, growing-up milks are designed with the intent to serve as a complement to a diverse diet to provide additional insurance that a child achieves continual, daily intake of all essential vitamins and minerals,

macronutrients plus additional functional dietary components, such as non-essential nutrients that have purported health-promoting properties.

[0165] The exact composition of a growing-up milk or other nutritional composition according to the present disclosure can vary from market-to-market, depending on local regulations and dietary intake information of the population of interest. In some embodiments, nutritional compositions according to the disclosure consist of a milk protein source, such as whole or skim milk, plus added sugar and sweeteners to achieve desired sensory properties, and added vitamins and minerals. The fat composition includes an enriched lipid fraction derived from milk. Total protein can be targeted to match that of human milk, cow milk or a lower value. Total carbohydrate is usually targeted to provide as little added sugar, such as sucrose or fructose, as possible to achieve an acceptable taste. Typically, Vitamin A, calcium and Vitamin D are added at levels to match the nutrient contribution of regional cow milk. Otherwise, in some embodiments, vitamins and minerals can be added at levels that provide approximately 20% of the dietary reference intake (DRI) or 20% of the Daily Value (DV) per serving. Moreover, nutrient values can vary between markets depending on the identified nutritional needs of the intended population, raw material contributions and regional regulations.

[0166] The disclosed nutritional composition(s) may be provided in any form known in the art, such as a powder, a gel, a suspension, a paste, a solid, a liquid, a liquid concentrate, a reconstituteable powdered milk substitute or a ready-to-use product. The nutritional composition may, in certain embodiments, comprise a nutritional supplement, children's nutritional product, infant formula, human milk fortifier, growing-up milk or any other nutritional composition designed for an infant or a pediatric subject. Nutritional compositions of the present disclosure include, for example, orally-ingestible, health-promoting substances including, for example, foods, beverages, tablets, capsules and powders. Moreover, the nutritional composition of the present disclosure may be standardized to a specific caloric content, it may be provided as a ready-to-use product, or it may be provided in a concentrated form. In some embodiments, the nutritional composition is in powder form with a particle size in the range of 5 μm to 1500 μm, more preferably in the range of 10 μm to 300μm.

[0167] The nutritional compositions of the present disclosure may be provided in a suitable container system. For example, non-limiting examples of suitable container systems include plastic containers, metal containers, foil pouches, plastic pouches, multi-layered pouches, and combinations thereof. In certain embodiments, the nutritional composition may be a powdered composition that is contained within a plastic container. In certain other

embodiments, the nutritional composition may be contained within a plastic pouch located inside a plastic container.

[0168] The nutritional compositions described herein, in some embodiments, advantageously reduce the incidence of allergic reaction and improve tolerance to cow's milk allergy in a subject. Further, in some embodiments, the nutritional compositions advantageously reduce the inflammatory response caused by allergy in a subject. Accordingly, the disclosure relates to methods of improving tolerance to cow's milk allergy in a subject. Further, the disclosure relates to methods of reducing the incidence of allergic reaction and reducing the inflammatory response caused by allergy in a subject via administration of the nutritional compositions including PDX/GOS and dietary butyrate as disclosed herein.

[0169] In some embodiments, the method comprises the step of subjecting the target subject to cow's milk and then providing the nutritional composition disclosed herein including PDX/GOS and dietary butyrate to the target subject. In certain embodiments, after the target subject has been subjected to cow's milk, the target subject may be provided with a nutritional composition that includes PDX/GOS and dietary butyrate and a protein equivalent source as disclosed herein. In certain embodiments, the target subject, after being exposed to cow's milk or other allergen, may be administered a nutritional composition comprising PDX/GOS and dietary butyrate, and a protein equivalent source. In certain embodiments, the protein equivalent source may be substantially free of whole and/or intact protein. In certain other embodiments, the protein equivalent source may comprise hydrolyzed protein, amino acids, the peptide component disclosed herein, and combinations thereof. In some embodiments, the nutritional composition includes a protein equivalent source includes amino acids and no hydrolyzed or whole/intact protein.

[0170] In some embodiments, the target subject is not subjected to cow's milk or an allergen prior to administration of the nutritional composition. Thus, in some embodiments, the method is directed to reducing allergic response in a target subject via providing the nutritional compositions disclosed herein including dietary butyrate to the target subject, and subsequently exposing the target subject to cow's milk or other allergen.

[0171] The nutritional compositions described herein, in some embodiments, advantageously reduce the inflammatory response in a subject. Accordingly, the disclosure relates to methods of reducing a proinflammatory response in a subject by administering to a subject a nutritional composition containing the protein equivalent source described herein in combination with PDX/GOS and dietary butyrate. For example, the present methods may reduce the production of proinflammatory cytokines in a subject.

[0172] In some embodiments, the method for reducing an inflammatory response in a subject comprises administering to a subject a nutritional composition comprising a

carbohydrate source, a protein equivalent source, fat source, PDX/GOS and dietary butryate, wherein the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63. In some embodiments, the peptide component may comprise additional peptides disclosed in Table 1. For example, the composition may include at least 10 additional peptides disclosed in Table 1. In some embodiments, 20% to 80% of the protein equivalent source comprises the peptide component, and 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, and combinations thereof.

[0173] In another embodiment, the method comprises administering to a subject a nutritional composition, wherein 20% to 80% of the protein equivalent source includes a peptide component comprising at least 3 peptides selected from the group consisting of SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63, and at least 5 additional peptides selected from Table 1; and wherein 20% to 80% of the protein equivalent source comprises an intact protein, a partially hydrolyzed protein, or combinations thereof.

[0174] In yet other embodiments, the method for reducing the inflammatory response includes providing a nutritional composition comprising a peptide component from Table 1, wherein the peptide component is derived from a casein hydrolysate having a molar mass distribution of greater than 500 Daltons. In some embodiments, the molar mass distribution of the casein hydrolysate is in a range of 500 to 2000 Daltons. In other embodiments, the method for reducing the inflammatory response includes providing a nutritional composition comprising the peptide component described herein, wherein the peptide component is derived from a casein hydrolysate that does not include peptides having a molar mass distribution of less than 200 Daltons.

[0175] In some embodiments the target subject may be a pediatric subject. Further, in one embodiment, the nutritional composition provided to the pediatric subject may be an infant formula. The peptide component identified herein, PDX/GOS and dietary butyrate as disclosed herein may be added to the infant formula and, further, each may be selected from a specific source and concentrations thereof may be adjusted to maximize health benefits. In another embodiment of this method, the nutritional composition comprising the peptide component disclosed herein, PDX/GOS and dietary butyrate is a growing up milk.

[0176] In embodiments when the nutritional composition is an infant formula, the composition may advantageously reduce a pro-inflammatory response in the infant, and thereby reduce the incidence of inflammatory disease. Moreover, the reduction in

inflammatory disease may last throughout childhood and into adulthood. Similarly, when the nutritional composition is a growing-up milk, a child who ingests the growing-up milk may experience a reduction in the incidence of inflammatory disease in adulthood, as well as during childhood.

[0177] In certain embodiments, the disclosure is directed to a method for improving the absorption of butyrate in a target subject by providing or administering the nutritional compositions disclosed herein including PDX/GOS and dietary butyrate to the target subject. In some embodiments, the target subject is a pediatric subject or an infant. In some embodiments, the nutritional composition is an infant formula or a growing-up milk.

[0178] All combinations of method or process steps as used herein can be performed in any order, unless otherwise specified or clearly implied to the contrary by the context in which the referenced combination is made.

[0179] The methods and compositions of the present disclosure, including components thereof, can comprise, consist of, or consist essentially of the essential elements and limitations of the embodiments described herein, as well as any additional or optional ingredients, components or limitations described herein or otherwise useful in nutritional compositions.

[0180] Formulation examples are provided to illustrate some embodiments of the nutritional composition of the present disclosure but should not be interpreted as any limitation thereon. Other embodiments within the scope of the claims herein will be apparent to one skilled in the art from the consideration of the specification or practice of the nutritional composition or methods disclosed herein. It is intended that the specification, together with the example, be considered to be exemplary only, with the scope and spirit of the disclosure being indicated by the claims which follow the example.

FORMULATION EXAMPLES

[0181] Table 3 provides an example embodiment of a peptide component including 8 peptides from Table1.

Table 3. Example peptide component

Example of Selected Peptides for Peptide Component
SEQ ID NO 5
SEQ ID NO 24
SEQ ID NO 33
SEQ ID NO 56
SEQ ID NO 64

SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60

[0182] Table 4 provides an example embodiment of a peptide component including certain peptides from Table 1.

Table 4. Example peptide component

Example of Selected Peptides for Peptide Component
SEQ ID NO 13
SEQ ID NO 24
SEQ ID NO 60
SEQ ID NO 5
SEQ ID NO 11
SEQ ID NO 22
SEQ ID NO 25
SEQ ID NO 33
SEQ ID NO 45
SEQ ID NO 46
SEQ ID NO 47
SEQ ID NO 48
SEQ ID NO 52
SEQ ID NO 34
SEQ ID NO 36
SEQ ID NO 61
SEQ ID NO 62
SEQ ID NO 64

[0183] Table 2 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 2 are based on a weight-to-weight percentage based on the total amino acids in the protein equivalent source.

Table 2. Example protein equivalent source

Amino Acid	w/w % amount based on total amino acids
L-leucine	9.94
L-lysine	7.93
L-valine	9.21
L-isoleucine	5.48
L-threonine	4.95
L-tyrosine	4.38
L-phenylalanine	4.05
L-histidine	2.12
L-cystine	2.12
L-tryptophan	1.93
L-methionine	1.87

[0184] Table 3 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 3 are based on a weight-to-weight percentage based on the total amino acids in the protein equivalent source.

Table 3. Example protein equivalent source

Amino Acid	w/w % amount based on total amino acids
L-aspartic acid	16.16
L-proline	8.05
L-alanine	7.87
Monosodium glutamate	5.54
L-serine	4.95
L-arginine	4.27
glycine	2.12

[0185] Table 4 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 4 are based on grams per 100 Kcal of the nutritional composition.

Table 4. Example protein equivalent source

Amino Acid (g)	per 100 Kcal

L-leucine	0.25
L-lysine	0.20
L-valine	0.23
L-isoleucine	0.14
L-threonine	0.12
L-tyrosine	0.11
L-phenylalanine	0.10
L-histidine	0.053
L-cystine	0.053
L-tryptophan	0.049
L-methionine	0.047

[0186] Table 5 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 5 are based on grams per 100 Kcal of the nutritional composition.

Table 5. Example protein equivalent source

Amino Acid (g)	per 100 Kcal
L-leucine	0.31
L-lysine	0.24
L-valine	0.28
L-isoleucine	0.17
L-threonine	0.15
L-tyrosine	0.13
L-phenylalanine	0.12
L-histidine	0.07
L-cystine	0.07
L-tryptophan	0.06
L-methionine	0.06

[0187] Table 6 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 6 are based on grams per 100 Kcal of the nutritional composition.

Table 6. Example protein equivalent source

Amino Acid (g)	per 100 Kcal
L-aspartic acid	0.41

L-proline	0.20
L-alanine	0.20
Monosodium glutamate	0.14
L-serine	0.13
L-arginine	0.11
Glycine	0.05

[0188] Table 7 provides an example embodiment of a protein equivalent source that may be included in the nutritional compositions disclosed herein. The amounts of amino acids disclosed in Table 7 are based on grams per 100 Kcal of the nutritional composition.

Table 7. Example protein equivalent source

Amino Acid (g)	**per 100 Kcal**
L-aspartic acid	0.50
L-proline	0.28
L-alanine	0.24
Monosodium glutamate	0.17
L-serine	0.15
L-arginine	0.13
Glycine	0.07

[0189] Table 8, illustrated below, provides an example embodiment of the nutritional profile of a nutritional composition including PDX/GOS and dietary butyrate and describes the amount of each ingredient to be included per 100 Kcal serving of nutritional composition.

Table 8. Nutrition profile of an example nutritional composition including dietary butyrate

	per 100 Kcal	
Nutrient		
	Minimum	**Maximum**
Protein Equivalent Source (g)	1.0	7.0
Dietary butyrate (mg)	22	280
Lactobacillus rhamnosus GG (cfu)	$1x10^4$	$1.5x10^{12}$
Carbohydrates (g)	6	22
Fat (g)	1.3	7.2
Prebiotic (g)	0.3	1.2

DHA (g)	4	22
Beta glucan (mg)	2.9	17
Probiotics (cfu)	0.5	5.0
Vitamin A (IU)	9.60×10^5	3.80×10^8
Vitamin D (IU)	134	921
Vitamin E (IU)	22	126
Vitamin K (mcg)	0.8	5.4
Thiamin (mcg)	2.9	18
Riboflavin (mcg)	63	328
Vitamin B6 (mcg)	68	420
Vitamin B12 (mcg)	52	397
Niacin (mcg)	0.2	0.9
Folic acid (mcg)	690	5881
Panthothenic acid (mcg)	8	66
Biotin (mcg)	232	1211
Vitamin C (mg)	1.4	5.5
Choline (mg)	4.9	24
Calcium (mg)	4.9	43
Phosphorus (mg)	68	297
Magnesium (mg)	54	210
Sodium (mg)	4.9	34
Potassium (mg)	24	88
Chloride (mg)	82	346
Iodine (mcg)	53	237
Iron (mg)	8.9	79
Zinc (mg)	0.7	2.8
Manganese (mcg)	0.7	2.4
Copper (mcg)	7.2	41

[0190] All references cited in this specification, including without limitation, all papers, publications, patents, patent applications, presentations, texts, reports, manuscripts, brochures, books, internet postings, journal articles, periodicals, and the like, are hereby incorporated by reference into this specification in their entireties. The discussion of the references herein is intended merely to summarize the assertions made by their authors and

no admission is made that any reference constitutes prior art. Applicants reserve the right to challenge the accuracy and pertinence of the cited references.

[0191] Although embodiments of the disclosure have been described using specific terms, devices, and methods, such description is for illustrative purposes only. The words used are words of description rather than of limitation. It is to be understood that changes and variations may be made by those of ordinary skill in the art without departing from the spirit or the scope of the present disclosure, which is set forth in the following claims. In addition, it should be understood that aspects of the various embodiments may be interchanged in whole or in part. Therefore, the spirit and scope of the appended claims should not be limited to the description of the versions contained therein.

CLAIMS

What is claimed is:

1. A nutritional composition comprising:

a carbohydrate source;

a protein equivalent source, wherein 1% to 99% of the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63; and 1% to 99% of the protein equivalent source comprises a partially hydrolyzed protein, an extensively hydrolyzed protein, or combinations thereof;

a fat or lipid source; and

at least one of the following:

(i) dietary butyrate;

(ii) a component for stimulating endogenous butyrate; or

(iii) combinations thereof.

2. The nutritional composition of claim 1, wherein the peptide component is present in an amount from about 0.2 g/100 Kcal to about 5.6 g/100 Kcal.

3. The nutritional composition of claim 1, wherein the peptide component further comprises at least 10 additional peptides selected from Table 1.

4. The nutritional composition of claim 1, wherein the protein equivalent source comprises partially hydrolyzed protein having a degree of hydrolysis of less than 40%.

5. The nutritional composition of claim 1, wherein the nutritional composition comprise dietary butyrate present in an amount of from about 22 mg/100 kcal to about 280 mg/100 kcal.

6. The nutritional composition of claim 1, comprising dietary butyrate, wherein the dietary butyrate comprises sodium butyrate.

7. The nutritional composition of claim 1, comprising dietary butyrate, wherein the dietary butyrate is provided by an enriched lipid fraction derived from milk.

8. The nutritional composition of claim 7, wherein the enriched lipid fraction derived from milk further comprises milk fat globule membrane.

9. The nutritional composition of claim 1, further comprising one or more long chain polyunsaturated fatty acids.

10. The nutritional composition of claim 9, wherein the one or more long chain polyunsaturated fatty acids comprises docosahexaenoic acid, arachidonic acid, and combinations thereof.

11. The nutritional composition of claim 1, further comprising one or more probiotics.

12. The nutritional composition of claim 1, further comprising β-glucan.

13. The nutritional composition of claim 1, wherein the nutritional composition is an infant formula.

14. A nutritional composition, comprising per 100 Kcal:

(i) between about 6 g and about 22 g of a carbohydrate source;

(ii) between about 1 g and about 7 g of a protein source, wherein 1% to 99% of the protein equivalent source includes a peptide component comprising SEQ ID NO 4, SEQ ID NO 13, SEQ ID NO 17, SEQ ID NO 21, SEQ ID NO 24, SEQ ID NO 30, SEQ ID NO 31, SEQ ID NO 32, SEQ ID NO 51, SEQ ID NO 57, SEQ ID NO 60, and SEQ ID NO 63; and 1% to 99% of the protein equivalent source comprises a partially hydrolyzed protein, and extensively hydrolyzed protein, or combinations thereof;

(iii) between about 1 g and about 10.3 g of a fat source;

(iv) between about 0.15 g and about 1.5 g of a prebiotic component comprising polydextrose and galacto-oligosaccharide; and

(v) between about 22 mg and 280mg of dietary butyrate.

15. The nutritional composition of claim 14, wherein the peptide component further comprises at least 10 additional peptides selected from Table 1.

16. The nutritional composition of claim 14, further comprising one or more long chain polyunsaturated fatty acids.

17. The nutritional composition of claim 14, further comprising one or more probiotics.

18. A nutritional composition comprising:

(i) a carbohydrate source;

(ii) a fat or lipid source;

(iii) a protein equivalent source, wherein the protein equivalent source comprises amino acids, wherein from about 10% to about 90% of the protein equivalent source comprises essential amino acids and wherein about 10% to about 90% of the protein equivalent source comprises non-essential amino acids; and at least one of the following:

(iv) dietary butyrate;

(v) a component for stimulating endogenous butyrate; or

(vi) combinations thereof.

19. The composition of claim 18, wherein the nutritional composition comprises one or more probiotics.

20. The composition of claim 18, wherein the nutritional composition is an infant formula.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/057646

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing:

   a. [X] forming part of the international application as filed:

      [X] in the form of an Annex C/ST.25 text file.

      [ ] on paper or in the form of an image file.

   b. [ ] furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. [ ] furnished subsequent to the international filing date for the purposes of international search only:

      [ ] in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      [ ] on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/057646

A. CLASSIFICATION OF SUBJECT MATTER
INV. A23L33/10 A23L33/12 A23L33/135 A23L33/18 A23L33/19
A23L33/21 A61P37/00
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 A61P

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)
EPO-Internal, WPI Data, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US 2014/271553 A1 (HONDMANN DIRK [US] ET AL) 18 September 2014 (2014-09-18) the whole document --- US 2014/271554 A1 (HONDMANN DIRK [US] ET AL) 18 September 2014 (2014-09-18) the whole document --- -/--	1-4,9-13 5-8, 14-20 1-13, 18-20

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

[X] 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 2016	03/01/2017

Name and mailing address of the ISA/	Authorized officer
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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2016/057646

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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