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NOURISHING PRODUCTS ENRICHED WITH NUCLEOSIDES AND/OR NUCLEOTIDES FOR INFANTS AND ADULTS AND PROCESSES FOR THEIR PREPARATION

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(57) Claim

1. A nutritionally balanced nourishing product, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by as added substance, adenosine and at least another nucleotide selected from the group consisting of uridine, guanosine, cytidine and inosine.

19. A method for the stimulation or repair and regeneration of intestinal cells in infants and adults, said method comprising the enteral administration of a nourishing product characterised by comprising at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

20. A method for enhancing the immune response of T-cells and for providing specific fatty acid phospholipid profiles in red blood cell membranes in infants and adults, said method comprising enterally administering to said infants and adults, a nourishing product containing at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

Nourishing Products Enriched with Nucleosides and/or Nucleotides for Infants and Adults and Processes for Their Preparation

The present invention relates to the composition and the preparation of nourishing products suitable for both infants and adults, particularly when dietetic or physiological deficiencies are present. These products are enriched with nucleosides, nucleotides, or mixtures thereof.

More specifically, said products, which may be administered orally or by enteral feeding, are adapted milks for pre-term infants, initial milks, follow-up milks, dietetic products, lactose free dietetic products and hypoalergenic dietetic products.

The European Society of Paediatric Gastroenterology and Nutrition (ESPGAN), the American Academy of Paediatric (AAP), the Codex Alimentarius Mundi, and the European Community Council, among other international organisations, have given general rules for the composition of infant formulas (ESPGAN Committee on Nutrition, Acta Paed. Scand, Supl 287, 1981; ESPGAN Committee on Nutrition, Acta Paed. Scand, Supl 302, 1982; ESPGAN Committee on Nutrition, Acta Paed. Scand, Supl 330, 1987; AAP Committee on Nutrition, Paediatric Nutrition Handbook, 1979; AAP Committee on Nutrition, Paediatrics, 75, 976, 1985; EEC Council, 85-C 28-05 COM (84) 703 in fine, 1985; EEC Council, 86-C 124-06 COM-86 91 in fine, 1986; Codex Alimentarius Mundi, Codex Stan 72-1981).

As used in this description, the term -infant formulas- refers to the milk and non-milk substances infant nutrition, particularly as defined by ESPGAN (Committee on Nutrition, Acta Paed. Scand., Supl. 262, p. 3, supra) and also the AAP (Paediatrics, Vol. 57 no 2, p. 281, February 1976).

Infant formulas are derived, to a large extent, from cow's milk. After being diluted, cow's milk is enriched with serum proteins diverse carbohydrates, such as lactose, dextrinmaltose and starches, different mixtures of vegetal and animal fats, vitamins and minerals, in suitable amounts to meet the requirements of low birth weight newborns or those of at-term healthy infants during the first and second semester of live.

Sometimes, infant formulas contain isolated milk proteins, isolated vegetal proteins or protein hydrolysates, from different origins such as casein, lactalbumin, soy and meat. Also, these infant formulas have one or more carbohydrates (sucrose, dextrinmaltose and starches), mixtures of diverse kind of fats, minerals and vitamins, to meet not only the healthy newborns' nourishing requirements, but also of infants and children with symptoms of lactose intolerance, protein intolerance and, in general, with diverse malabsorption-malnutrition syndromes.

Usually, infant formulas tend to have a composition qualitatively and quantitatively as similar as possible to human milk. Nevertheless, despite the efforts made by several researchers, infant formulas still have a number of differences in their composition compared to human milk. This is because the latter has many substances, such as immunoglobulins, free amino acids, polyamines, nucleotides, polyunsaturated fatty acids,

etc., which are not present in cow's milk. Thus it would be desirable that infant milk formulas have most of the substances present in human milk so as to produce the same physiological effects as human milk.

Regarding nutritional products for adults, specially for dietary purposes, even in hospitals, are based on the utilisation of diverse protein sources (casein, sodium and calcium caseinates, isolated soy proteins, protein hydrolysates and/or crystalline amino acids) mixtures of vegetal and animal fats, carbohydrates (basically glucose polymers), vitamins and minerals to meet, at least, the dietary intakes recommended for healthy individuals (Committee on Dietary Allowances, Food and Nutrition Board, Nat. Acad. Sci. 9th Ed, 1980).

Protein energy malnutrition (PEM) is found in many patients admitted to hospitals. This happens not only in developing countries, but also in those with a high socioeconomic level where the percentages of medical-surgical patients vary between 40-50% (B. Bistrian *et al.* JAMA, 235, 1567, 1976; G. Hill *et al.* Lancet, 1, 689, 1977; Gassull *et al.* Human Nutr.: Clin. Nutr. 38C, 419, 1984). Proper nutritional support for such patients, while not a primary mode of treatment is, nevertheless, an important factor for therapy and recovery. It is, therefore important to administer a nutritionally balanced diet given orally, enterally or parenterally, adequate to the needs of the patient. This is specially true for those patients where conventional feeding is contraindicated (gastroenterological patients) or is insufficient (hypercatabolic patients). The enteral or oral mode of administration of foods is preferable to parenteral modes (E. Cabre and M.A. Gassull, J. Clin. Gastroenterol. Nutr., 1, 97, 1986) because of the lower morbidity, trophic effect upon the intestinal mucosa, lower necessity for instruments and lower costs.

Dietetic products for proper nourishment of patients are formulated to meet the requirements of those individuals in specific situations. Thus, complete balanced diets with an energy content between 130-150Kcal/g nitrogen, are recommended for the preventive and repletive therapy in cases of PEM due to nervous anorexia, oesophageal stenosis, maxillofacial surgery, chronic vasculo-cerebral disease, long evolution neurological syndromes, vascular surgery postoperative period, malabsorption syndromes, preoperative period, incomplete intestinal occlusion, preparation of colon (surgery, radiology and endoscopy) and, in general, in all cases when it is necessary to take a balanced diet of nutrients. Diets with a high content of nitrogen (80-120Kcal/g nitrogen) are recommended for the nutritional therapy of burn patients or patients suffering cranial trauma, multiple trauma, open fractures, Crohn disease, ulcerous colitis, digestive fistula, sepsis, oncology surgery, oncological radiotherapy and chemotherapy, pre- and postoperative periods, orthopaedic surgery, and, in general, for catabolic patients.

Diets containing protein hydrolysates as a source of amino nitrogen are specially made for the nutritional support of patients with diverse malabsorption-malnutrition syndromes, such as short bowel, acute celiac disease, Crohn disease, chronic pancreatic insufficiency, cystic fibrosis, intestinal fistulas, postoperative nutrition, and the like.

Furthermore, such products can be made as specific clinical diets for specific diseases, such as hepatopathies, chronic renal disease, and chronic obstructive pulmonary disease.

In addition, there is a variety of dietary products marketed to meet the nutritional needs of various individuals. For example, many individuals desirous of achieving varying degrees of weight loss, may benefit from the use of a special nutrition diet formulation to provide specific nutrients otherwise provided by a normal diet. Likewise, many people find it necessary to supplement their daily diet with additional nutrients due to age, allergy or physical afflictions.

As used herein, the terms diets, formulas and nutritionally balanced products are intended to refer to the aforementioned types of products.

Currently marketed nutrition products do not contain nucleic acids or their simpler compounds -nucleosides and/or nucleotides- which are normally present in foods and carry out fundamental physiological functions described further on.

In relation to the nutritional importance of nucleotides, some relevant aspects of these compounds such as their content in human milk, physiological effects in newborns, intestinal absorption, tissue utilisation and effects upon cell immunity are shown below.

US 4 544 559 teaches that human milk has a specific nucleotide content, very different from cow's milk. Human milk contains, at least, twelve different nucleotides, predominating CMP (cytidine monophosphate), AMP (adenosine monophosphate), UMP (uridine monophosphate), GMP (guanosine monophosphate), IMP (inosine monophosphate) and uridine derivatives, whereas cow's milk has very low amounts of CMP and AMP it lacks the other nucleotides and has high amounts of orotic acid, which is absent in human milk.

Also, US 4 544 559 teaches that a humanised milk enriched with nucleotides (AMP, CMP, GMP, UMP, IMP) in the same range as human milk, stimulates the development of *Bifidobacterium bifidum* Ti at the intestinal level. This bacterium comprises 80% of the total bifidobacteria present in the faeces of breast-fed newborns. Furthermore, this humanised milk promotes a serum fatty acid profile very similar to tnat found in newborns fed with human milk.

US 3 231 385 describes infant milk formulas supplemented with certain nucleotides to simulate human milk, improve the milk taste and lower the curd tension.

Nucleotides can be synthesised in most tissues by two processes: (a) *de novo* synthesis from the precursors which include pirophosphoribosilphosphate, glutamine, aspartate, glycine, formiate and carbon dioxide, and (b) utilisation of the bases and nucleosides liberated through the catabolism of nucleotides and nucleic acids contained in foods. This last way, called salvage pathway, is an important alternative when biosynthetic de novo pathways are hindered by an insufficient supply of precursors. Tissues such as bone marrow, intestine and liver are heavily dependent on said salvage

pathway. The activity of the salvage pathway has also been shown demonstrated in kidney, brain and retina.

The intestinal mucosa needs a continuous supply of nucleotides or their precursors from dietary origin, apart from the hepatic supply by the vascular system, in order to maintain continuous synthesis of RNA

It has been confirmed in cuts made in the small intestine of rats that the exogenous ATP (adenosine triphosphate) increases the intracellular concentration of this nucleotide and it has been observed that at temperatures over 20°C the marked exogenous ATP is absorbed by everted sacs of rat small intestine. Also, it has been shown in rabbit's ileum "*in vitro*" that, at low concentrations, the ATP as well as the nucleoside adenosine are absorbed through a carrier associated to the enterocyte membrane.

Since the carrier system works for ATP and adenosine, it is likely that the system also works for other purine nucleotides, because competitive inhibition measures have proved that any compound with a purine ring united to a ribose molecule is absorbed

It has also been shown that the purines and pyrimidines in the RNA and DNA, present in the diet, are absorbed by mice, preferably as nucleosides. Between 2-5% of the nucleosides are used for nucleic acid synthesis in intestinal tissue, and citosine nucleosides are used for DNA synthesis, specially in the spleen. Further, it has been shown that purine bases, such as adenine, guanine, hypoxanthine and xanthine are almost completely absorbed by rats, 4.5-6.5% being incorporated in tissues and in a greater proportion by the liver and intestine.

The absence of pyrimidine or purine derivatives in the diet is known to suppress the normal function of T-lymphocytes (F. Rudolph *et al.* Adv. Exp. Med. Biol., 165,175, 1984), and to increase the mortality in experimental animals by staphylococcus sepsis. The addition of pyrimidine and purine derivatives to the diet decreases the susceptibility of animals to infection (A. Kulkarni *et al*, JPEN, 10, 169, 1986). Thus, the effect of purines and pyrimidines on the immune function can be of great importance in a number of clinic situations, such as transplants of organs in patients, malnutrition recovery, in diverse chemotherapeutic regimens and in the treatment of leukemias derived from T-cells.

Accordingly, one of the objects of the present invention is to provide improved nutritionally balanced diet formulations.

Another object of the present invention is to provide improved non-milk or milk based infant formulas which not only closely resemble human milk, but which are more readily absorbed by the infant gut and enhance the infant's immune response.

These and other objects of the present invention will become more apparent from the description which follows.

The present invention provides a range of compositions of infant formulas and adults nutrition products enriched with nucleosides, nucleotides or mixes of these two

classes of compounds and the processes for their preparation. The products are in a liquid ready to eat form, or concentrated liquid or powder.

According to a first embodiment of this invention, there is provided a nutritionally balanced nourishing product, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by as added substance, adenosine and at least another nucleotide selected from the group consisting of uridine, guanosine, cytidine and inosine.

According to the invention, adenosine, guanosine, cytidine, inosine, and uridine or their mixes are used as nucleosides, and adenosine phosphate, guanosine phosphate, cytidine phosphate, inosine phosphate and uridine phosphate or their mixes are used as nucleotides.

The term uridine phosphate, guanosine phosphate, etc., is intended hereinbefore to refer collectively to the mono, di and/or tri phosphate as well as the sugar derivatives of the nucleotides mentioned. However, for various reasons which will be apparent to those knowledgeable in the art, the 5'-monophosphates are the preferred nucleotides.

The supplementation of nucleosides and/or nucleotides or their mixes to infant formulas and nutrition balanced diet formulations gives a better physiological fatty acid tissue membrane composition to newborns and adults, an improved cell immunity and a better intestinal repair in those individuals with intestinal diseases.

According to a second embodiment of this invention, there is provided a nutritionally balanced nourishing product in powder form, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitam characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, and at least the mixture of one of the following nucleosides and cc esponding nucleotides: uridine and uridine phosphate; guanosine and guanosine phosphate; cytidine and cytidine phosphate, or inosine and inosine phosphate, wherein the total combined nucleoside and nucleotide content is in the range of 50 to 1250mg for each 100g of product.

According to a third embodiment of this invention, there is provided a nutritionally balanced nourishing product in liquid form, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, at least the mixture of one of the following nucleosides and corresponding nucleotides: uridine and uridine phosphate; guanosine and guanosine phosphate; cytidine and cytidine phosphate, or inosine and inosine phosphate, wherein the total combined nucleoside and nucleotide content is in the range of 10 to 250mg for each decilitre of product.

Thus, the product must contain at least one of the fifteen different possible components. Generally, the product will contain from 1 to 300mg (based on 100g of dry product) of the aforesaid components, with a preferred range being from about 50 to about 250mg. The optimum amount appears to be about 150mg per 100g of product.

On a liquid basis, these ranges correspond to from about 0.2 to 60mg/dL, and preferably about 10 to about 50mg/dL, with the optimum being about 30mg/dL.

According to a fourth embodiment of this invention, there is provided a cow's milk free infant formula comprising carbohydrates, a source of amino acids, vegetable oils, minerals and vitamins, characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, at least one of the following substances: uridine, uridine phosphate or mixtures thereof; guanosine, guanosine phosphate or mixtures thereof; cytidine, cytidine phosphate or mixtures thereof, or inosine, inosine phosphate or mixtures thereof.

A further embodiment of the invention provides for improved non-milk infant formulas. Such non-milk formulas are well known and generally comprise carbohydrates, a source of amino acids, vegetable oils, minerals and vitamins. According to the invention, there is added to such formulas at least one of the following substances: uridine, uridine phosphate or mixtures thereof; guanosine, guanosine phosphate or mixtures thereof; adenosine, adenosine phosphate or mixtures thereof; cytidine, cytidine phosphate or mixtures thereof, or inosine, inosine phosphate or mixtures thereof.

As a minimum, at least about 0.27mg per 100g of product of one of said compounds should be added to the infant formula. Generally, the non-milk infant formulas according to the invention require on a dry weight basis in mg per 100g of product the following quantities: uridine and/or uridine phosphate 17.40-1.86mg; guanosine and/or guanosine phosphate 3.32-0.27mg; adenosine and/or adenosine phosphate 9.50-4.25mg; cytidine and/or cytidine phosphate 10.16-3.52mg, and inosine and/or inosine phosphate 1.92-0.00mg.

On a liquid basis, per dL, these formulations generally correspond as follows: uridine and/or uridine phosphate 2.62-0.28mg; guanosine and/or guanosine phosphate 0.50-0.04mg; adenosine and/or adenosine phosphate 1.43-0.64mg; cytidine and/or cytidine phosphate 1.53-0.53mg, and inosine and/or inosine phosphate 0.29-0.00mg.

For reasons discussed more fully below, it may be desirable to add small amounts of L-cystine and/or carnitine to the non-milk based infant formulas.

According to a fifth embodiment of this invention, there is provided an infant milk formula containing cow's milk, sugars, vegetable oils, minerals and vitamins, characterised by further comprising at least one nucleoside selected from the group consisting of uridine, guanosine, adenosine, cytidine and inosine.

The added nucleosides must be present in an amount about 0.27mg per 100g of product on a dry basis. To provide for a closer simulation of human breast milk and also enhance absorption by the infant gut, these should be added to the infant milk formula the

following approximate quantities for each 100g of product: uridine and/or uridine phosphate 17.40-1.86mg; guanosine and/or guanosine phosphate 3.32-0.27mg; adenosine and/or adenosine phosphate 3.75-0.00mg; cytidine and/or cytidine phosphate 4.58-0.00mg, and inosine and/or inosine phosphate 1.92-0.00mg.

On a liquid basis the corresponding quantities per dL will be as follows: uridine and/or uridine phosphate 2.62-0.28mg; guanosine and/or guanosine phosphate 0.50-0.04mg; adenosine and/or adenosine phosphate 0.56-0.00mg; cytidine and/or cytidine phosphate 0.69-0.00mg, and inosine and/or inosine phosphate 0.29-0.00mg.

According to a sixth embodiment of this invention, there is provided a method for the stimulation or repair and regeneration of intestinal cells in infants and adults, said method comprising the enteral administration of a nourishing product characterised by comprising at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

According to a seventh embodiment of this invention, there is provided a method for enhancing the immune response of T-cells and for providing specific fatty acid phospholipid profiles in red blood cell membranes in infants and adults, said method comprising enterally administering to said infants and adults, a nourishing product containing at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

According to an eighth embodiment of this invention, there is provided a process for the preparation in liquid form and aseptic packaging of nourishing products enriched with nucleosides and/or nucleotides, having a composition according to the invention characterised by comprising the steps of:

Mixing water and non-fat solids, in the absence of any vitamins, nucleosides and nucleotides; Preheating the mixture to a temperature ranging from 75 to 80°C; Deaerating of the said mixture; Injection of a mixture of edible fats in the deaerated mixture; Homogenising the mixture under pressure; Cooling of the mixture in the range of 4-6°C; Standardising the mixture by addition of those nucleosides, nucleotides, vitamins, minerals and other components not added in first step, adjusting the pH in the range of 6.8 to 7.1; UHT sterilising of the standardised mixture; Homogenising of the mixture under pressure followed by cooling, and Aseptic packaging of the obtained product.

According to a ninth embodiment of this invention, there is provided a process for the preparation in liquid form and bottling of nourishing products enriched with nucleosides and/or nucleotides, having a composition according to the invention, characterised by comprising the steps of: Mixing water and non-fat solids, in the absence of any vitamins, nucleosides and nucleotides; Preheating the mixture to a temperature ranging from 75 to 80°C; Deaerating of the said mixture; Injection of a mixture of edible fats in the deaerated mixture; Homogenising the mixture under pressure; Cooling of the mixture in the range of 4-6°C; Adjusting pH in the range of 6.8 to 7.1; UHT sterilising

of the adjusted mixture; Standardising of the sterilised mixture by addition of those nucleosides, nucleotides, vitamins, minerals and other components not added in first step; Reheating of the standardised mixture to 30-70°C; Bottling of the reheated mixture, and Sterilising the final bottled product.

According to a tenth embodiment of this invention, there is provided a process for the preparation in powder form of nourishing products enriched with nucleosides and/or nucleotides, having a composition according to the invention, characterised by comprising the steps of: Mixing water with the non-fat solids, in the absence of the vitamins, nucleosides and nucleotides; Preheating the mixture to a temperature ranging from 75 to 80°C; Deaerating of the said mixture; Injection of a mixture of edible fats in the deaerated mixture; Homogenising the mixture under pressure; Cooling of the mixture in the range of 4-6°C; Standardising of the cooled mixture by addition of those nucleosides, nucleotides, vitamins, minerals and other components not added in first step, adjusting the pH in the range of about 6.8 to about 7.1; Reheating of the standardised mixture to 65 to 70°C; Homogenising of the reheated mixture under pressure; Drying in a spray drier, and Packaging of the obtained product.

Basically, infant formulas, according to the invention have a composition adequate for meeting the requirements of low birth weight infants, at-term infants, children with lactose intolerance, children with cow's milk protein intolerance or children with diverse malabsorption syndromes.

The infants formulas and nutritionally balanced diet products of the present invention have been found to stimulate repair and regeneration of intestinal gut cells, enhance the immune response of T-cells and provide for specific fatty acid phospholipids profiles in red blood cell membranes.

The use of nucleosides is a characterising feature of the products according to the invention. These materials generally have been found to be at least as effective as their corresponding nucleotides, and even more effective in providing for enhanced absorption through use of the salvage pathway in the human body, since nucleotides present in the diet first need to be hydrolysed into nucleosides. However, this process is not carried out under a quantitative pattern and, therefore, must be concluded the higher bioavailability of nucleosides when compared to nucleotides, together with the synergism produced when both nucleosides and nucleotides are mixed. This action may be due to the higher water solubility of nucleosides as compared to the corresponding nucleotides. A food supplemented with nucleotides may vary in its nucleotide composition along the time, if it is processed in such a way that phosphatases from residual microorganisms can exert their enzymatic action. This can occur, for example, in pasteurised products and in spray-dried products. However, a food supplemented with nucleosides maintain its specific nucleoside composition for all its commercial life.

When nucleosides and/or nucleotides or their combinations are added to infant formulas in concentrations in the same range as human milk, according to this invention,

they stimulate the conversion of essential fatty acids to their polyunsaturated fatty acids (PUFA), which is reflected in the fatty acid composition of erythrocyte membrane both in the at-term newborn and in the pre-term newborn as well as in the fatty acids composition of plasma phospholipids.

In study carried out by the inventors, 20 at-term newborns were fed exclusively on human milk, 19 with a conventional infant formula and 19 with the same infant formula supplemented with nucleotide-5'-monophosphates according to this invention, in similar concentrations to those of human milk. The relative content of PUFA, of the w6 series, derived from linoleic acid, as well as ω3 series, derived from linolenic acid, was significantly decreased, specially in phosphatidylethanolamine and phosphatidylserine of the erythrocyte membrane in infants fed conventional milk formula with respect to infants fed nucleotide-5'-monophosphates supplemented milk formula or human milk. The same happened in the plasma phospholipids and cholesteryl esters. The arachidonic (20:4ω6) and docosahexaenoic (22:6ω3) acids were the most increased fatty acids in infants fed nucleotide-5'-monophosphates supplemented milk formula, with respect to those fed conventional milk formula.

In another study, 19 pre-term infants were fed exclusively on human milk, 18 with an infant milk formula for premature infants and 18 with the same milk formula supplemented with nucleotides-5'-monophosphates in concentrations similar to those of human milk, according to this invention. At one month of life, the relative contents of eicosatrienoic acid (20:3ω6), arachidonic acid (20:4ω6), docosatetraenoic acid (22:4ω6) and docosapentaenoic acid (22:5ω6) were significantly decreased in the erythrocyte membrane phospholipids in infants fed milk formula with respect to those fed nucleotide-5'-monophosphate supplemented milk formula or human milk. Also, infants fed nucleotide-5'-monophosphate supplemented milk formula showed an intermediate value of docosahexaenoic acid (22:6ω3) between those fed human milk and those fed milk formula. The same results were observed in the plasma phospholipids of pre-term newborns.

The modulating effect of nucleosides and nucleotides of the diet upon cell immunity has been proved through the following method:

Six groups of BALB-C mice, constituted by 10 mice each, aged four weeks, weaning period, were fed with a conventional diet, a nucleosides and nucleotides free diet, a diet supplemented with nucleosides according to this invention, in the following proportions: 50mg of uridine, 50mg or guanosine, 50mg of adenosine, 50mg of cytidine and 50mg of inosine, a diet supplemented with nucleosides in proportions equivalent to mouse milk, a diet supplemented with 50mg of the following nucleotides UMP, GMP, CMP, AMP and IMP according to this invention and a diet supplemented with nucleotides in proportions equivalent to mouse milk, respectively. The mice were fed during a period of four weeks, and it was carried out with them the testing of the cell immune response "*in vitro*" as response to allogeneic and syngeneic antigens using the lymphocyte mixed

culture technique and quantifying the cell proliferation by the incorporation of 3H-thymidine to DNA and secondly was carried out the testing of the proliferation as response to phytohaemaglutinin (mitogen agent) to quantify the state of lymphocyte reactivity also with the incorporation of 3H-thymidine.

The mice fed on the free nucleoside or nucleotide diets had an immune response mediated by T-cells lower than the other groups having a diet supplemented with these compounds.

The effects of nucleosides and nucleotides of the diet on the intestinal cell proliferation and on their enzymatic activity is proved as follows:

Two groups of Wistar mice, of 20 animals each, from the weaning (21 days of age), are fed during two weeks, the first of them on a diet (Diet A) containing 167g of calcium caseinate, 489.5g of corn starch, 150g of sugar, 50g of cellulose, 100g of soy oil, 3g of DL-methionine, 1.1g of choline chloride, 38.2g of a mineral mixture and 1.2g of a vitamin mixture, per kg, to satisfy the nutritional requirements of these animals. The second group was fed with a similar diet, but with lactose instead of starch (Diet B). In this second group takes place an osmotic diarrhoea because of lactose intolerance giving rise to a malnutrition-malabsorption syndrome. Both groups are divided in two subgroups of 10 animals each, the first subgroup being fed on Diet A 2nd the second with on Diet A supplemented with 50mg of each of the following nucleosides: uridine, guanosine, adenosine, cytidine and inosine, during 4 weeks or with 50mg of each or the following nucleotides: UMP, GMP, AMP, CMP and IMP according to this invention.

The animals suffering malabsorption syndrome refed on the nucleoside or nucleotide supplemented diet, according to the invention, had ileal, jejunal and duodenal mucosa weight significantly superior to those fed on a diet without such compounds. Also, the proportion of cells in a mitosis state, the mucosa protein content and the maltase and sucrase enzymatic activities were significantly higher in animals fed on the nucleoside or nucleotide supplemented diet than in those fed on a diet without such compounds.

Basic ingredients for infant formulas include cow's milk, proteins, whey proteins, casein and its salts (ie. calcium caseinate), soy protein isolates are used in the products made for infants with lactose intolerance and/or cow's protein intolerance. Protein hydrolysates (ie. casein and lactalbumin hydrolysates) with low molecular weight, may also be used for the products made for the treatment of infant malabsorption syndromes.

The proportions of the diverse component nutrients are similar to those of human milk. Thus, the ratio of whey proteins to casein currently varies from 60:40 to 70:30 in infant formulas based on milk. The mixture of fats employed is made up of edible fats to provide an essential fatty acids profile. Lactose is used exclusively as the carbohydrate source for at-term newborns infants, except that dextrinmaltose is employed in products used for the treatment of lactose intolerance and malabsorption syndromes in infancy.

Infant formulas according to the invention contain minerals (including calcium, phosphorus, sodium, potassium, chloride, magnesium, iron, zinc, copper, manganese and

iodine) and vitamins (including vitamin A, D_3, C, B_1, B_2, B_6, B_{12}, pantothenic acid, E, K_1, folic acid, biotin) adequate for the infants' requirements. Also, in the products whose source or proteins is derived from soy or protein isolates or hydrolysates, carnitine is included to satisfy the nutritional requirement for this compound in infants with malabsorptive syndromes.

The inventors of the present compositions and processes have demonstrated that the amounts of citosine, adenine, guanine, uracil and inosine derivatives in human milk, expressed as CMP, AMP, GMP, UMP and IMP, vary between 1.53-0.54, 1.43-0.69, 0.50-0.12, 2.62-1.40 and 0.29-0.00mg/dL respectively and the individual contents of CMP, AMP, GMP, UMP and IMP oscillate between 1.73-0.53, 1.19-0.64, 0.21-0.04, 0.56-0.28, 0.29-0.00mg/dL, respectively.

The content of nucleosides and/or nucleotides in the infant formulas of the present invention are in the range of those for human milk. An exemplary nucleoside and/or nucleotide mixture for infant formulas not containing cow's milk, according to the invention, is shown in Table 1.

Table 1

Content of nucleosides and/or nucleotides in infant formulas without cow's milk.

	Powdered product		Liquid product	
		Range		Range
Nucleosides and/or Nucleotides	mg/100g		mg/dL	
Uridine/Uridine phosphate	3.42	17.40-1.86	0.51	2.62-0.28
Guanosine/Guanosine phosphate	1.49	3.32-0.27	0.22	0.50-0.04
Adenosine/Adenosine phosphate	6.90	9.50-4.25	1.03	1.43-0.64
Cytidine/Cytidine phosphate	6.87	10.16-3.52	1.03	1.53-0.53
Inosine/Inosine phosphate	1.00	1.92-0.00	0.15	0.29-0.00

The amounts of adenosine and/or adenosine phosphate, cytidine and/or cytidine phosphate, inosine and/or inosine phosphate added to cow's milk based infant formulas, according to this invention, are lower than those shown in Table 1, because cow's milk contains specific amounts of said compounds. Table 2 is an exemplary mixture of nucleosides and/or nucleotides for infant milk formulas containing cow's milk.

Table 2

Content of nucleosides and/or nucleotides in infant formulas with cow's milk.

	Powdered Product Range	Liquid product Range
Nucleosides and/or Nucleotides	mg/100g	mg/dL
Uridine/Uridine phosphate	17.40-1.86	2.62-0.28
Guanosine/Guanosine phosphate	3.32-0.27	0.50-0.04
Adenosine/Adenosine phosphate	3.75-0.00	0.55-0.00
Cytidine/Cytidine phosphate	4.58-0.00	0.69-0.00
Inosine/Inosine phosphate	1.92-0.00	0.29-0.00

The dietary products for balanced nutrition of adults, according to the invention, have a composition of nutrients adequate to the specific requirements of not only healthy human in need of a balanced nutritional product, but also those individuals in situations of energy-protein malnutrition and in hypercatabolic states derived from traumatic, septic, surgical processes and malabsorption syndromes.

As nitrogenous sources, the following components are preferably employed: a mixture of dairy proteins (casein or sodium and calcium caseinates and lactose free lactalbumin) and protein hydrolysates with low molecular weight (maximum molecular weight 1000 Daltons, average molecular weight 500 Daltons). As carbohydrate sources, glucose polymers are employed, such as dextrinmaltose with a different grade of dextrose equivalent degree, preferably between 10 and 30DE. Fats are employed as a mixture of animal and one or more vegetable fats to meet the essential fatty acids requirements.

As nutritional products for adults according to the present invention provide mineral elements which include trace element and vitamins in adequate proportions to satisfy the specific requirements of normal healthy individuals as well as those suffering malabsorption-malnutrition processes and in a hypercatabolic state

The nutritional products are enriched with nucleosides and/or nucleotides in similar amounts of nucleotides to those present in foods.

An example of a nucleoside and/or nucleotide mixture for the enrichment of nutritionally balanced products is shown in Table 3.

Table 3

Content of nucleosides and/or nucleotides in nutritionally balanced products of adults.

	Powdered product		Liquid product	
		Range		Range
Nucleosides and/or Nucleotides	mg/100g		mg/dL	
Uridine/Uridine phosphate	150	1-300	30	0.2-60
Guanosine/Guanosine phosphate	150	1-300	30	0.2-60
Adenosine/Adenosine phosphate	150	1-300	30	0.2-60
Cytidine/Cytidine phosphate	150	1-300	30	0.2-60
Inosine/Inosine phosphate	150	1-300	30	0.2-60

In a dry weight basis, the amount of nucleosides and/or nucleotides may each vary from 1 to 300mg per 100g of product, and preferably the total ranges from 50 to 1250mg per 100g of product. On a liquid basis the amount may vary from 0.2 to 60mg/dL of each nucleoside and/or nucleotide, and preferably the total ranges from 10 to 250mg.

The invention also includes the processes to obtain infant formulas, as well as specific diets to be used in good nutrition, enriched with nucleosides and/or nucleotides.

The products can be prepared in liquid, ready to be used, concentrated to be diluted in water before its use, and in powder forms.

These processes comprise, in all cases, the preparation of a mixture containing water and non fat solids, except vitamins, some minerals and nucleosides and/or nucleotides, followed by a preheating to 75-80°C, deaeration of the mixture, injection of the fat mixture, double homogenisation at 70-75°C (usually 150kPa in the first stage and 50kPa in the second) cooling to 4-6°C and storage in standardisation tanks.

The liquid products ready for consumption or concentrates to be diluted before use, are standardised in the said tanks, adapting the pH to values generally ranging from 6.8 to 7.1 and most preferably ranging from 6.8 to 7.0 for infant formulas and from 6.9 to 7.1 for adult nutritional products.

When the products are going to be UHT (ultra-high temperature) sterilised and aseptically packed in containers made of carton-aluminium-polyethylene, during the standardisation, the vitamins, minerals and nucleosides or nucleotides mixtures are added as concentrated aqueous solutions and the content of mineral elements is adjusted by adding the required salts. The nucleoside and/or nucleotide solutions should be maintained preferably at pH 6-6.5 to avoid them to hydrolyse.

Once standardised, the products for consumption in liquid or concentrated forms, are sterilised through an UHT system at 145-150°C for 2-4 seconds and can be either aseptically packed or bottled in glass or polyethylene bottles. In the latter case, products are standardised prior to the UHT sterilisation, only in their solids contents, and the pH is adjusted to values equivalents as noted above; immediately after they are sterilised, refrigerated at 4-6°C and stored in standardisation tanks, the vitamins, minerals and the nucleoside and/or nucleotide solutions are added; afterwards the products are reheated at 30-70°C, packed in polyethylene or glass bottles, and sterilised in a continuous steriliser at 120-121°C for 10 minutes.

In the case of powder products, after the phases concentrated solids recombination, preheating, deaeration, fat mixture injection, homogenisation, refrigeration, final pH standardisation, concentration and addition of vitamins, minerals nucleosides and/or nucleotides, the mixture is reheated to 65-70°C, homogenised at 100-150kg/cm^2 and dried in a spray drier. Afterwards, the powdered product is packed in polyethylene-aluminium containers or in cans, internally coated with varnish, under inert atmosphere, or in other acceptable containers.

A better understanding of the processes of the invention will be obtained from the detailed description which follows, given in relation to the accompanying drawing, in which: Figure 1 is a schematic view of plant manufacturing process for preparing products of the present invention.

Following the schema of said figure, the general process and its alternatives are described in more detail below.

Example A

Through the heat exchanger (1), deionised water is fed to storage tanks (2), at a temperature between 60-70°C. Through the centrifugal pump (3) and tri-blender (4) non fat solids (proteins, carbohydrates and some minerals) are dissolved being maintained the temperature at 60-65°C by means of heat exchanger (5).

The resulting mixture is fed through positive pump (6) to filters (7) and heat exchanger (8), to be heated to 75-80°C for 15-20s to get the product pasteurised; being immediately deaerated in a vacuum deaerator (9), lowering the temperature to 70-75°C. Afterwards, the deaerated product is fed through centrifugal pump (10) and mixed with fat through fat injector (15). The mixture of fats stored in tank (12) has been fed through positive pump (13) to the heat exchanger (14) to be heated at 70-75°C before reaching fat injector (15). A retention valve (11) prevents the product which contains the non fat solids and fat to go back to the deaerator. Immediately after fats are mixed to the non fat solids mixture, the product is homogenised at (16) at a temperature of about 70-75°C and 200-300kg/cm^2 of total pressure, in two stages (1st stage 150-200kg/cm^2, 2nd stage 50-100kg/cm^2).

For liquid products which are to be aseptically packaged, after homogenisation in (16), they are cooled to 4-6°C in plate heat exchanger (917) and fed to the pair of isothermal standardising tanks (18) where the pH is adjusted to from about 6.8 to about 7.1 depending on the product desired. Vitamins, minerals, nucleosides and/or nucleotides in the required amounts are fed to (18) and the resulting mixture is fed by pumps (19) and (20) to a UHT steriliser (21) at 145-150°C during 2-4s, and homogenised in (22) (preferably in a double stage at 80°C and 200-250kg/cm^2), then is cooled to 20-25°C in heat exchanger (23) and aseptically packaged in (36), ie. brick type packs of cardboard, aluminium and polyethylene.

For liquid products which are to be bottled, the process is the same as above through the cooling treatment in (17). Then the pH is adjusted in tanks (18) to above noted values. The mixture is fed by pumps (19) and (20) for UHT sterilisation at (21) and homogenisation at (22). The sterilised mixture is cooled in (23) and fed directly to standardising tanks (32) where vitamins, minerals, nucleosides and/or nucleotides as required are added. From tanks (32), and by means of pump (33), the mixture is fed to reheater (34) where the temperature is raised to about 30°C for polyethylene bottles to 70°C for glass bottles. The product is bottled in a filling machine (35) and subjected to sterilisation in (37) at a temperature of about 120-121°C for about 10 to 15 minutes.

For powder products, the process is the same as above through homogenisation in (16). As shown by the dotted line in the figure, the product is fed to heat exchanger (24) and cooled to about 4 to about 6°C and fed to isothermal standardising tanks (25), where the pH is adjusted and the required vitamins, minerals, nucleosides and/or nucleotides are added. Then the standardised product is pumped by (26) through filters (27) and fed to reheater (28) where the temperature is raised to about 65 to about 70°C, and then filtered

in (29) and homogenised at (30) under a pressure of about 100-200kg/cm^2. The homogenised product is fed to a spray drying tower (31) and collected for packaging.

The invention will be readily understood from the following examples, which; are not to he construed as limiting the scope of the invention.

Example 1

This example provides a product made to feed pre-term and low birth weight infants, enriched with nucleosides and/or nucleotides according to the invention. Basically, the product is a mixture of cow's milk, demineralised serum proteins, dextrinmaltose, fat mixture, minerals, vitamins and nucleosides and/or nucleotides mixture.

The product has been adapted in the proteins, fat carbohydrates, minerals and vitamins contents to the ESPGAN and AAP international recommendations as related to the feeding of low birth weight infants (ESPGAN, Committee on Nutrition, Acta Paediatr. Scand., 1987 (in press); AAP, Committee on Nutrition, Paediatrics, 1985).

Table 4

	For 100g powder	For 100mL liquid
Ingredients:		
Water	----	85%
Maltodextrins	28.91%	4.33%
Vegetable oils mixture	20.23%	3.03%
Skim milk (0.05% fat)	14.58%	2.19%
Lactalbumin	12.13%	1.82%
Lactose	11.92%	1.79%
Butterfat	6.45%	0.97%
Minerals	3.26%	0.49%
Calcium caseinate	1.97%	0.296%
Lecithin	0.41%	0.061%
Vitamins	0.12%	0.018%
Nucleosides and/or nucleotides	0.0078%	0.0012%
Ascorbile palmitate	0.006%	0.0009%
DL-αTocopherol	0.001%	0.0001%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	515µg
Guanosine and/or guanosine monophosphate	1.49mg	225µg
Adenosine and/or adenosine monophosphate	1.32mg	200µg
Cytidine and/or cytidine monophosphate	1.12mg	170µg
Inosine and/or inosine monophosphate	0.45mg	70µg
Mineral salts added:		
Calcium lactate	1.74g	0.26g
Sodium phosphate dibasic	0.65g	97mg
Calcium phosphate	0.36g	54mg
Potassium chloride	0.23g	34mg

Potassium phosphate dibasic	0.17g	26mg
Ferrous lactate	51.7mg	7.6mg
Magnesic sulfate	49mg	7.3mg
Zinc sulfate	7.3mg	1.1mg
Cupric sulfate	1.9mg	285µg
Sodium fluoride	1.5mg	225µg
Potassium and chromium sulfate	510µg	76µg
Sodium molybdate	265µg	40µg
Sodium selenite	180µg	27µg
Manganese sulfate	83µg	12µg
Potassium iodide	64µg	10µg
Vitamins added:		
Vitamin A	1600IU	240IU
Vitamin D	600IU	90IU
Vitamin E	5.5mg	825µg
Vitamin K	60µg	9µg
Thiamine	0.4mg	60µg
Riboflavin	0.45mg	65µg
Pyridoxine	0.25mg	37µg
Niacin	6.7mg	1mg
Calcium pantothenate	5.5mg	825µg
Vitamin B12	1.1µg	0.16µg
Biotin	15µg	2.2µg
Folic acid	350µg	52µg
vitamin C	100mg	15mg

Example 2

This example provides a milk formula made to feed at-term infants, during the first year of life, preferably for the 6 first months of lactation, supplemented with nucleosides and/or nucleotides in similar concentrations to those of human milk, according to the invention.

The product has been adapted in its composition and content of nutrients to the ESPGAN and AAP international recommendations for this kind of infants (ESPGAN, Committee on Nutrition, Acta Paediatr. Scad., Supl. 262, 1977 AAP, Committee on Nutrition, Paediatric Nutrition Handbook, 1979).

Table 5

	For 100g powder	For 100mL liquid
Ingredients:		
Water	----	87%
Lactose	42.61%	5.54%
Vegetable oils	13.37%	1.74%
Powdered milk (26% fat)	25.47%	3.31%
Demineralised whey (65% proteins)	9.28%	1.21%

Butterfat	7.77%	1.01%
Mineral salts	1.11%	0.14%
Lecithin	0.31%	0.04%
Vitamins	0.069%	0.009%
Nucleosides and/or nucleotides	0.0078%	0.001%
Ascorbile palmitate	0.001%	0.0001%
DL-αTocopherol	0.003%	0.0004%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	445μg
Guanosine and/or guanosine monophosphate	1.49mg	195μg
Adenosine and/or adenosine monophosphate	1.32mg	170μg
Cytidine and/or cytidine monophosphate	1.12mg	145μg
Inosine and/or inosine monophosphate	0.45mg	58μg
Mineral salts added:		
Tricalcium citrate	0.31g	40mg
Tripotassium citrate	0.35g	45mg
Calcium chloride	0.16g	21mg
Dibasic potassium phosphate	0.24g	31mg
Ferrous lactate	39mg	5.1mg
Zinc acetate	8.5mg	1.1mg
Cupric sulfate	1.10mg	143μg
Manganese sulfate	155μg	20μg
Potassium iodide	65μg	8.4μg
Vitamins added:		
Vitamin A	1600IU	208IU
Vitamin D	300IU	39IU
Vitamin E	5.5mg	715μg
Vitamin K1	60μg	7.8μg
Calcium pantothenate	5.5mg	715μg
Vitamin B12	1.1μg	0.14μg
Biotin	15μg	1.9μg
Folic acid	25μg	3.2μg
Vitamin C	50mg	6.5mg
Nicotinamide	6.7mg	870μg
Vitamin B2	450μg	58μg
Vitamin B1	400μg	52μg
Vitamin B6	300μg	35μg

Example 3

This example provides an infant milk formula made to feed healthy infants from 4-5 months to one year of live, supplemented with nucleosides and/or nucleotides, according to the invention. The product has been adapted in its composition and content of nutrients to the ESPGAN recommendations for these infants (ESPGAN, Committee on Nutrition, Acta Paediatr. Scan. Supl. 287. 1981).

Table 6

	For 100g of powder	For 100mL of liquid
Ingredients		
Water	----	85%
Lactose	19.28%	2.89%
Vegetable oils mixture	6.08%	0.91%
Full milk	46.61%	6.99%
Maltodextrins	23.18%	3.48%
Demineralised whey	4.22%	0.63%
Mineral salts	0.41%	0.061%
Lecithin	0.14%	0.021%
Vitamins	0.069%	0.01%
Nucleosides and/or nucleotides	0.0078%	0.0012%
Ascorbile palmitate	0.001%	0.0001%
DL-αTocopherol	0.003%	0.0004%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	515µg
Guanosine and/or guanosine monophosphate	1.49mg	225µg
Adenosine and/or adenosine monophosphat.	1.32mg	200µg
Cytidine and/or cytidine monophosphate	1.12mg	170µg
Inosine and/or inosine monophosphate	0.45mg	70µg
Mineral salts added:		
Monocalcium phosphate	0.36g	54mg
Ferrous lactate	39mg	5.8mg
Zinc acetate	8.5mg	1.3mg
Cupric sulfate	1.1mg	165µg
Manganese sulfate	155µg	23µg
Potassium iodide	65µg	9.7µg
Vitamins added:	As in Example 2.	

Example 4

This example provides a lactose free infant formula, containing protein from milk origin, supplemented with nucleosides and/or nucleotides in the same quantities as in human milk, according to the invention.

The product has been adapted in its composition and content of nutrients to the international recommendations mentioned before.

Table 7

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	85%
Vegetable oils mixture	10.35%	1.55%
Maltodextrins	58.03%	8.7%
Calcium caseinate + L-cystine	16.7%	2.51%

Butterfat	11.96%	1.79%
Mineral salts	2.18%	0.33%
Lecithin	0.69%	0.103%
Vitamins	0.069%	0.01%
Carnitine	0.0089%	0.0013%
Nucleosides and/or nucleotides	0.0078%	0.0012%
DL-αTocopherol	0.003%	0.0004%
Ascorbile palmitate	0.001%	0.0001%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	515µg
Guanosine and/or guanosine monophosphate	1.49mg	225µg
Adenosine and/or adenosine monophosphate	3.32mg	500µg
Cytidine and/or cytidine monophosphate	4.98mg	750µg
Inosine and/or inosine monophosphate	1.00mg	150µg
Mineral salts added:		
Dibasic potassium phosphate	588mg	88mg
Ferrous lactate	48mg	7.2mg
Tripotassium citrate	522mg	78mg
Zinc acetate	11.2mg	1.7mg
Cupric sulfate	1.15mg	0.17mg
Manganese sulfate	107µg	16µg
Potassium iodide	65µg	9.7µg
Calcium lactate	272mg	41mg
Sodium chloride	389mg	58mg
Magnesium chloride	260mg	39mg
Vitamins added	As in Example 2.	
Other substances added:		
L-cystine	0.1g	15µg
Carnitine	8.9mg	1.3mg

Example 5

This example provides a lactose free adapted infant formula containing a protein isolate .from vegetal origin, supplemented with nucleosides and/or nucleotides, according to the invention.

The product has been adapted, as in Example 4, in its composition and content of nutrients to the suckling children and newborns.

Table 8

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	85%
Vegetable oils mixture	10.35%	1.55%
Maltodextrins	57.20%	8.58%
Soy protein isolate	16.67%	2.5%
Butterfat	11.96%	1.79%

Mineral salts	3.04%	0.46%
Lecithin	0.69%	0.103%
Vitamins	0.069%	0.01%
Carnitine	0.0089%	0.0013%
Nucleosides and/or nucleotides	0.0078%	0.0012%
Ascorbile palmitate	0.001%	0.0001%
DL-αTocopherol	0.003%	0.0004%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	515μg
Guanosine and/or guanosine monophosphate	1.49mg	225μg
Adenosine and/or adenosine monophosphate	3.32mg	500μg
Cytidine and/or cytidine monophosphate	4.98mg	750μg
Inosine and/or inosine monophosphate	1.00mg	150μg
Mineral salts added:		
Dibasic potassium phosphate	450mg	67.5mg
Ferrous lactate	48mg	7.2mg
Tripotassium citrate	628mg	94.2mg
Zinc acetate	11.2mg	1.7mg
Cupric sulfate	1.18mg	0.18mg
Manganese sulfate	107μg	25μg
Potassium iodide	65μg	9.7μg
Calcium lactate	873mg	131mg
Calcium chloride	370mg	55.5mg
Magnesium chloride	260g	39mg
Calcium carbonate	400mg	60mg
Vitamins added:	As in Example 2.	
Other substances added		
Carnitine	8.9mg	1.3mg

Example 6

This example provides a lactose free infant formula which contains a mixture of lactalbumin and casein hydrolysates with a low molecular weight, supplemented with nucleosides and/or nucleotides, as specified in the invention.

The composition and content of nutrients are adapted to the nursing children and newborns' requirements, as in Examples 4 and 5.

Table 9

	For 100g of powder	For 100mL of liquid
Ingredients:		
water	----	85%
Vegetable oils mixture	16.98%	2.55%
Maltodextrins	52.48%	7.87%
Lactalbumin enzymatic hydrolysate	12.31%	1.85%
Casein enzymatic hydrolysate	5.16%	0.77%
Corn starch	4.87%	0.73%

Butterfat	4.29%	0.64%
Mineral salts	3.19%	0.48%
Emulsifier	0.60%	0.09%
Lecithin	0.0231%	0.0035%
Vitamins	0.069%	0.01%
Carnitine	0.0089%	0.0013%
Nucleosides and/or nucleotides	0.0078%	0.0012%
Ascorbile palmitate	0.0015%	0.0002%
DL-αTocopherol	0.0038%	0.0006%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	3.42mg	515µg
Guanosine and/or guanosine monophosphate	1.49mg	225µg
Adenosine and/or adenosine monophosphate	3.32mg	500µg
Cytidine and/or cytidine monophosphate	4.98mg	750µg
Inosine and/or inosine monophosphate	1.00mg	150µg
Mineral salts added:		
Dibasic potassium phosphate	0.12g	18mg
Ferrous lactate	39mg	5.8mg
Tripotassium citrate	0.85g	0.13g
Zinc acetate	10mg	1.5mg
Cupric sulfate	2.2mg	330µg
Manganese sulfate	307µg	46µg
Potassium iodide	65µg	9.7µg
Calcium phosphate	0.86g	0.13g
Calcium chloride	0.49g	73mg
Magnesium sulfate	0.20g	30mg
Sodium phosphate dibasic	0.38g	57mg
Potassium chloride	0.24g	36mg
Sodium fluoride	310µg	46.5µg
Potassium and chromium sulfate	115µg	17µg
Sodium molybdate	83µg	12µg
Sodium selenite	37µg	5.5µg
Vitamins added:	As in Example 2.	
Other substances added:		
Carnitine	8.9mg	1.3mg

The products in Examples 4, 5 and 6 contain carnitine in similar concentration to that found in human milk to satisfy the newborns' requirements of this compound.

The products in Examples 1 to 6 are presented as liquid products, ready to use, as liquid concentrate products, to be used with the addition of water and as powdered products.

Example 7

Example 7 provides a complete product and nutritionally balanced to be used orally or by feeding tubes, with an energy ratio of 146Kcal/g nitrogen, enriched with nucleosides and/or nucleotides in agreement with the invention.

The composition and content of nutrients have been adapted to the specific nutritional requirements of adults suffering energy-protein malnutrition.

Table 10

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	78.7%
Vegetable oils mixture	12.1%	2.5%
Maltodextrins	52.13%	51.2%
Lactalbumin	11.63%	2.48%
Calcium, caseinate	16.05%	2.14%
Butterfat	8.84%	1.88%
Mineral salts	3.79%	0.79%
Emulsifier	----	0 136%
Stabiliser	----	0.02%
Soy lecithin	0.66%	----
Vitamins	0.026%	0.005%
Nucleosides and/or nucleotides	0.75%	0.15%
Ascorbile palmitate	0.02326%	0.0008
DL-αTocopherol	0.0008%	0.0002%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	150mg	30mg
Guanosine and/or guanosine monophosphate	150mg	30mg
Adenosine and/or adenosine monophosphate	150mg	30mg
Cytidine and/or cytidine monophosphate	150mg	30mg
Inosine and/or inosine monophosphate	150mg	30 mg
Mineral salts added:		
Sodium phosphate dibasic	1.1g	270mg
Ferrous lactate	21mg	4mg
Dibasic potassium phosphate	0.28g	34mg
Zinc acetate	14mg	3mg
Cupric sulfate	3mg	640µg
Manganese sulfate	4mg	760µg
Potassium iodide	49µg	10µg
Calcium chloride	0.31g	58mg
Magnesium sulfate	1.014g	203mg
Potassium chloride	0.99g	210mg
Sodium fluoride	2.2mg	442µg
Potassium and chromium sulfate	480µg	96µg
Sodium molybdate	315µg	63µg
Sodium selenite	166µg	33µg
Sodium chloride	50mg	6mg

Vitamins added:		
Vitamin A	250µg	50µg
Vitamin D	2.5µg	0.5µg
Vitamin E	2.5mg	0.5mg
Vitamin K1	35µg	7µg
Pantothenic acid	1.75mg	0.35mg
Vitamin B12	0.75µg	0.15µg
Biotin	50µg	10µg
Folate	100µg	20µg
Vitamin C	15mg	3mg
Niacin	4.75mg	0.95mg
Vitamin B2	425µg	85µg
Vitamin B1	375µg	75µg
Vitamin B6	550µg	110µg

Example 8

This example provides a complete product and nutritionally balanced with a high protein content (91Kcal/g nitrogen), enriched with nucleosides and/or nucleotides in agreement with the invention.

The composition and content of nutrients have been adapted to meet the specific nutritional requirements of adults in hypercatabolic state.

Table 11

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	77.28%
Vegetable oils mixture	9.13%	1.99%
Maltodextrins	50.6%	11.49%
Lactalbumin	15.96%	3.64%
Calcium caseinate	13.08%	3.14%
Butterfat	6.52%	1.49%
Mineral salts	3.41%	0.68%
Emulsifier	----	0.11%
Stabiliser	----	0.02%
Soy lecithin	0.5%	----
Vitamins	0.026%	0.005%
Nucleosides and/or nucleotides	0.75%	0.15%
Ascorbile palmitate	0.0232%	0.0008%
DL-αTocopherol	0.0008%	0.0002%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	150mg	30mg
Guanosine and/or guanosine monophosphate	150mg	30mg
Adenosine and/or adenosine monophosphate	150mg	30mg
Cytidine and/or cytidine monophosphate	150mg	30mg
Inosine and/or inosine monophosphate	150mg	30mg

Mineral salts added:		
Sodium phosphate dibasic	0.88g	180mg
Ferrous lactate	21mg	4mg
Dibasic potassium phosphate	0.19g	30mg
Zinc acetate	14mg	3mg
Cupric sulfate	3mg	640µg
Manganese sulfate	4 mg	760µg
Potassium iodide	49µg	10µg
Calcium chloride	0.11g	5mg
Magnesium sulfate	1.014g	203mg
Potassium chloride	1.01g	220mg
Sodium fluoride	2.2mg	442µg
Potassium and chromium sulfate	480µg	96µg
Sodium molybdate	315µg	63µg
Sodium selenite	166µg	33µg
Sodium chloride	0.16g	40mg
Vitamins added:	As in Example 7.	

Example 9

This example provides a complete product and nutritionally balanced, with a high nitrogen content, using as source of this element a protein hydrolysate with a low molecular weight to make easier its absorption, enriched with nucleosides and/or nucleotides according to the invention. The energy ratio of this product is 100Kcal/g nitrogen.

The composition and content of nutrients have been adapted to satisfy the specific nutritional requirements of adults suffering diverse malabsorption-malnutrition syndromes.

Table 12

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	77.83%
Vegetable oils mixture	12.44%	2.76%
Maltodextrins	51.62%	11.43%
Casein hydrolysate	25.80%	5.72%
Butterfat	3.62%	0.8%
Mineral salts	5.02%	1.11%
Emulsifier	----	0.11%
Stabiliser	----	0.02%
Soy lecithin	0.50%	----
Vitamins	0.026%	01.0058%
Nucleosides and/or nucleotides	0.75%	0.17%
L-cystine	0.20%	0.04%
Ascorbile palmitate	0.0232%	0.0051%
DL-αTocopherol	0.0008%	0.0002%

Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	150mg	30mg
Guanosine and/or guanosine monophosphate	150mg	30mg
Adenosine and/or adenosine monophosphate	150mg	30mg
Cytidine and/or cytidine monophosphate	150mg	30mg
Inosine and/or inosine monophosphate	150mg	30mg
Mineral salts added:		
Sodium phosphate dibasic	1.05g	233mg
Ferrous lactate	21mg	4.6mg
Dibasic potassium phosphate	0.80g	177mg
Zinc acetate	14mg	3.1mg
Cupric sulfate	3mg	665µg
Manganese sulfate	4mg	888
Potassium iodide	49µg	11µg
Calcium chloride	0.84g	186mg
Magnesium sulfate	1.014g	225mg
Sodium fluoride	2.2mg	488µg
Potassium and chromium sulfate	480µg	106µg
Sodium molybdate	315µg	70µg
Sodium selenite	166µg	37µg
Sodium chloride	0.44g	97mg
Tripotassium citrate	0.83g	184mg
Vitamins added:	As in Example 7	
Other substances added:		
L-cystine	200mg	40mg

Example 10

This example provides a complete product and nutritionally balanced with a low protein content, supplemented with branched chain amino acids and enriched with nucleosides and/or nucleotides, according to the invention.

The composition and content of nutrients have been adapted to satisfy the specific nutritional requirements of adults suffering severe hepatopathy.

Table 13

	For 100g of powder	For 100mL of liquid
Ingredients:		
Water	----	76.36%
Vegetable oils mixture	7.48%	1.77%
Maltodextrins	72.13%	17.04%
Lactalbumin	7.26%	1.72%
Calcium caseinate	6.27%	1.48%
Mineral salts	2.94%	0.69%
Emulsifier	----	0.05%
Stabiliser	----	0.01%

Soy lecithin	0.22%	----
Vitamins	0.026%	0.006%
Nucleosides and/or nucleotides	0.75%	0.18%
L-leucine	1.16%	0.27%
L-valine	0.87%	0.21%
L-isoleucine	0.87%	0.21%
Ascorbile palmitate	0.0197%	0.005%
DL-αTocopherol	0.00034	0.00007%
Nucleosides and/or nucleotides added:		
Uridine and/or uridine monophosphate	150mg	30mg
Guanosine and/or guanosine monophosphate	150mg	30mg
Adenosine and/or adenosine monophosphate	150mg	30mg
Cytidine and/or cytidine monophosphate	150mg	30mg
Inosine and/or inosine monophosphate	150mg	30mg
Mineral salts added:		
Sodium phosphate dibasic	0.60g	142mg
Ferrous lactate	21mg	5mg
Dibasic potassium phosphate	0.67g	158mg
Zinc acetate	14mg	3.3mg
Cupric sulfate	3mg	709µg
Manganese sulfate	4mg	946µg
Potassium iodide	49µg	11.6µg
Calcium chloride	0.49g	116mg
Magnesium sulfate	1.014g	240mg
Sodium fluoride	2.2mg	520µg
Potassium and chromium sulfate	480µg	113µg
Sodium molybdate	315µg	74µg
Sodium selenite	166µg	39µg
Sodium chloride	0.12g	28mg
Vitamins added:	As in Example 7.	
Other substances added:		
L-leucine	1.16g	274mg
L-valine	870mg	206mg
L-isoleucine	870mg	206mg

Example 11

This example provides a product considered as a nutritional supplement for the nutritional repletion of adults with chronic hepatopathy, constituted by a mixture of proteins from milk origin, supplemented with branched chain amino acids, carbohydrates, vitamins and minerals and enriched with nucleosides and/or nucleotides.

Table 14

	For 100g powder	For 100mL liquid
Ingredients:		
Water	----	80.00%
Maltodextrins	36.72%	7.32%

Lactalbumin	26.26%	5.25%
Sodium caseinate	21.95%	4.39%
Mineral salts	3.2%	0.64%
Vitamins	0.026%	0.005%
Nucleosides and/or nucleotides	0.75%	0.15%
L-leucine	4.04%	0.81%
L-valine	3.03%	0.61%
L-isoleucine	3.03%	0.61%
Nucleosides and/or Nucleotides added:		
Uridine and/or uridine monophosphate	150mg	30mg
Guanosine and/or guanosine monophosphate	150mg	30mg
Adenosine and/or adenosine monophosphate	150mg	30mg
Cytidine and/or cytidine monophosphate	150mg	30mg
Inosine and/or inosine monophosphate	150mg	30mg
Mineral salts added:		
Sodium phosphate dibasic	0.36g	72mg
Ferrous lactate	21mg	4.2mg
Dibasic potassium phosphate	0.17g	34mg
Zinc acetate	14mg	2.8mg
Cupric sulfate	3mg	600µg
Manganese sulfate	4mg	800µg
Potassium iodide	49µg	9.8µg
Calcium chloride	0.38g	76µg
Magnesium sulfate	1.014g	203mg
Sodium fluoride	2.2mg	440µg
Potassium and chromium sulfate	480µg	96µg
Sodium molybdate	315µg	63µg
Sodium selenite	166µg	33µg
Potassium chloride	0.89g	178mg
Tripotassium citrate	0.34g	68mg
Vitamins added:	As in Example 7.	
Other substances added:		
L-leucine	4.04g	810mg
L-valine	3.03g	610mg
L-isoleucine	3.03g	610mg

The invention having been thus described, it will be appreciated by those in the art that variations can occur within the scope of claims which follow.

The claims defining the invention are as follows:

1. A nutritionally balanced nourishing product, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by as added substance, adenosine and at least another nucleotide selected from the group consisting of uridine, guanosine, cytidine and inosine.

2. A product according to claim 1, in powder form, characterised by containing for each 100 g: uridine 1-300mg; guanosine 1-300mg; adenosine 1-300mg; cytidine 1-300mg, and inosine 1-300mg.

3. A product according to claim 2, characterised by containing: uridine 50-250mg; guanosine 50-250mg; adenosine 50-250mg; cytidine 50-250mg, and inosine 50-250mg.

4. A product according to claim 1, in liquid form, characterised by containing per decilitre: uridine 0.2-60mg; guanosine 0.2-60mg; adenosine 0.2-60mg; cytidine 0.2-60mg, and inosine 0.2-60mg.

5. A product according to claim 4, characterised by containing: uridine 10-50mg; guanosine 10-50mg; adenosine 10-50mg; cytidine 10-50mg, and inosine 10-50mg.

6. A nutritionally balanced nourishing product in powder form, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, and at least the mixture of one of the following nucleosides and corresponding nucleotides: uridine and uridine phosphate; guanosine and guanosine phosphate; cytidine and cytidine phosphate, or inosine and inosine phosphate, wherein the total combined nucleoside and nucleotide content is in the range of 50 to 1250mg for each 100g of product.

7. A nutritionally balanced nourishing product in liquid form, specially suitable for the preparation of infant formulas and dietetic products for adults, which contains a source of amino nitrogen, carbohydrates, edible fats, minerals and vitamins, characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, at least the mixture of one of the following nucleosides and corresponding nucleotides: uridine and uridine phosphate; guanosine and guanosine phosphate; cytidine and cytidine phosphate, or inosine and inosine phosphate, wherein the total combined nucleoside and nucleotide content is in the range of 10 to 250mg for each decilitre of product.

8. A cow's milk free infant formula comprising carbohydrates, a source of amino acids, vegetable oils, minerals and vitamins, characterised by further comprising, as added substance, adenosine, adenosine phosphate or mixtures thereof, at least one of the following substances: uridine, uridine phosphate or mixtures thereof; guanosine, guanosine phosphate or mixtures thereof; cytidine, cytidine phosphate or mixtures thereof, or inosine, inosine phosphate or mixtures thereof.

9. A formula according to claim 8, characterised by comprising on a dry basis per 100g: up to 17.40mg of uridine, uridine phosphate or mixtures thereof; up to 03.32mg of guanosine, guanosine phosphate or mixtures thereof; up to 03.75mg of adenosine, adenosine phosphate or mixtures thereof; up to 04.58mg of cytidine, cytidine phosphate or mixtures thereof, and up to 01.92mg of inosine, inosine phosphate or mixtures thereof.

10. A formula according to claim 8, characterised by its powdered form.

11. A formula according to claim 9, characterised by containing per 100 g of total weight: uridine and/or uridine phosphate 17.40-1.86mg; guanosine and/or guanosine phosphate 3.32-0.27mg; adenosine and/or adenosine phosphate 9.50-4.25mg; cytidine and/or cytidine phosphate 10.16-3.52mg, and inosine and/or inosine phosphate 1.92-0.00mg.

12. A formula according to claim 8, characterised by its liquid form.

13. A formula according to claim 12, characterised by containing per decilitre of liquid product: uridine and/or uridine phosphate 2.62-0.28mg; guanosine and/or guanosine phosphate 0.50-0.04mg; adenosine and/or adenosine phosphate 1.43-0.64mg; cytidine and/or cytidine phosphate 1.53-0.53mg, and inosine and/or inosine phosphate 0.29-0.00mg.

14. A formula according to claim 9, characterised by containing L-cystine.

15. A formula according to claim 11, characterised by containing L-cystine.

16. A formula according to claim 9, characterised by containing carnitine.

17. A formula according to claim 11, characterised by containing carnitine.

18. An infant milk formula containing cow's milk, sugars, vegetable oils, minerals and vitamins, characterised by further comprising as added substance, adenosine and at least another nucleoside selected from the group consisting of uridine, guanosine, cytidine and inosine.

19 A method for the stimulation or repair and regeneration of intestinal cells in infants and adults, said method comprising the enteral administration of a nourishing product characterised by comprising at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

20. A method for enhancing the immune response of T-cells and for providing specific fatty acid phospholipid profiles in red blood cell membranes in infants and adults, said method comprising enterally administering to said infants and adults, a nourishing product containing at least one of the following nucleosides, nucleotides or mixtures thereof: uridine, uridine phosphate, guanosine, guanosine phosphate, adenosine, adenosine phosphate, cytidine, cytidine phosphate, inosine and inosine phosphate.

21. A formula according to claim 18, characterised by containing for each 100g of powder product: uridine and uridine phosphate 17.40-1.86mg; guanosine and guanosine

phosphate 3.32-0.27mg; adenosine and adenosine phosphate 3.75-0.00mg; cytidine and cytidine phosphate 4.58-0.00mg, and inosine and inosine phosphate 1.92-0.00mg.

22. A formula according to claim 18, characterised by containing per decilitre of liquid product: uridine and uridine phosphate 2.62-0.28mg; guanosine and guanosine phosphate 0.50-0.04mg; adenosine and adenosine phosphate 0.56-0.00mg; cytidine and cytidine phosphate 0.69-0.00mg, and inosine and inosine phosphate 0.29-0.00mg.

23. A nutritionally balanced nourishing product specially suitable for the preparation of infant formulas and dietetic products for adults, substantially as hereinbefore described with reference to any one of examples 1 to 10.

24. A cow's milk free infant formula comprising carbohydrates, a source of amino acids, vegetable oils, minerals and vitamins substantially as hereinbefore described with reference to example 5 or 6.

25. An infant milk formula containing cow's milk, sugars, vegetable oils, minerals and vitamins substantially as hereinbefore described with reference to any one of examples 1 to 3.

26. A method of enhancing immune response in an infant requiring such enhancement, comprising administering to said infant an effective amount of a formula as defined in claim 24 or 25.

27. A method of alleviating or treating protein energy malnutrition in a patient requiring such alleviation or treatment, comprising administering to said patient an effective amount of a nutritionally balanced nourishing product as defined in claim 23.

Dated 15 July, 1997
Abbott Laboratories

Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

Nourishing Products Enriched with Nucleosides and/or Nucleotides for Infants and Adults and Processes for Their Preparation

Abstract

This invention relates to milk and non-milk infant formulas, as well as nourishing products for adults, which contain a source of amino nitrogen, carbohydrates, edible fats, minerals, vitamins and further comprises at least one nucleoside selected from the group consisting of uridine, guanosine, adenosine, cytidine and inosine. The processes for the preparation of these products is also described in which deionised water and dissolved fats are heated (1) (5), mixed (6) (7) and pasteurised (8), before dearation (9). Fats are then added through an injector (15) and the mixture is homogenised (16). If the formula is to be aseptically packaged, the pH is adjusted together with the addition of vitamins, minerals, nucleosides and/or nucleotides (18) before sterilisation (22), cooling (23) and packaging (36). If liquid products are to be bottled, the vitamins etc are added in standardising tanks (32) before reheating (34) and bottling (37). A powder product is obtained by adding the vitamins etc in standardising tanks (25), filtering (29) homogenising and spray drying (31).

Figure 1.

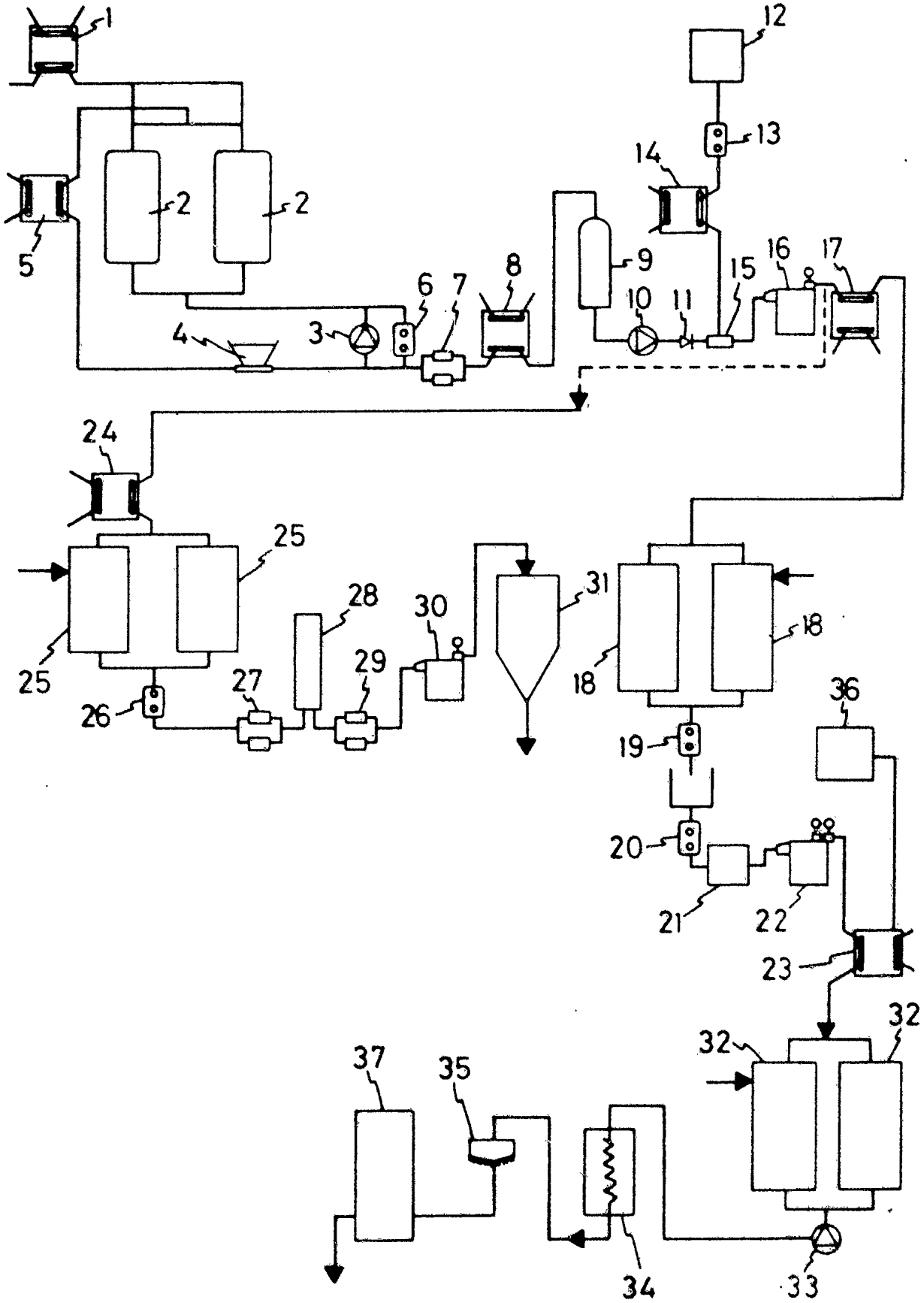
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Fig.1