U.S. WHEY PRODUCTS AND CHILD NUTRITION

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*The value of breast milk as an ideal food for the infant during the first six months of its life cannot be too strongly stressed. However, poor health of the mother and certain social conditions can reduce lactation, separate the infant from the mother or otherwise make breastfeeding impossible. In these circumstances, it is necessary to use alternative foods such as infant formula to overcome the lack of breast milk.**

Please consult a physician or dietician for use of formulas for infant and child nutrition. All formulations and compositional information for infant formulas are provided for general information and demonstration purposes only. Adjustments may be required. Please check local regulations for product standards, the use of product names and specific ingredients.

*Statement on Infant Feeding. Codex Standards for Foods for Infants and Children, Codex Alimentarius, 1989.

INTRODUCTION

Whey protein is widely used as a high quality protein source and as a source of active peptides in healthy foods. Infant formula manufacturers are increasingly adding whey proteins to cow's milk-based infant formulas to match the high concentration of whey proteins as found in human milk, and to formulas for infants with special needs including fussiness, colic and allergy to cow's milk protein. While literature supportive of the use of whey proteins in infant formula for fussiness and colic is limited, there are numerous peer-reviewed reports on the use of hydrolyzed whey protein for milk protein allergy. In the case of milk protein allergy, the utilization of hydrolyzed whey protein is motivated by its high biologic value and superior taste and smell, compared to casein hydrolysates. Benefits of supplementing infant formulas with whey protein are discussed in the following sections.

BACKGROUND

Human milk is widely considered to be the ideal feeding for newborn infants. Its composition is thought to have resulted from the effects of time and evolution on nutritional compromise between mother and infant. Thousands of years ago antibodies directed at pathogens encountered by the mother were certainly important for the survival of the infant. Human milk also contains an incredible array of functional enzymes, growth factors, gastrointestinal protective factors, functional immune cells and non-protein nitrogen sources. Changes in composition occurring over the course of lactation render human milk a remarkably complex infant food.

The ultimate goal of an infant formula manufacturer cannot possibly be to match this amazing complexity using industrial cow's milk preparations. Rather, their goal is to make the second best infant feeding available by targeting the major differences between human milk and infant formulas. Cow's milk protein-based infant formulas are relied upon to provide optimal nutritional support for infants that, for a variety of reasons, cannot be, or are not, breastfed.

Comparatively, limited numbers of infants are fed formulas based on protein sources other than milk. Yet some of the desirable components of human milk (pathogen-specific human milk IgA) are either too variable or costly to be considered for addition to infant formula. Cow's milk itself does not match the superb, evolutionary adaptation of human milk to the nutritional needs of the infant. One of the primary compositional gaps between human milk and cow's milk-based infant formula is the difference in whey protein content. Technical advances in milk protein chemistry have led to a number of solutions to this 'deficiency' in cow's milk-based infant formulas.

Table 1. Human and Cow Milk Whey Proteins[1]

Whey Protein	Human Milk (% of whey protein)	Cow Milk (% of whey protein)
Lactoferrin	23.8	10-100[2]
α-Lactalbumin	30.2	19.3
β-lactoglobulin	—	51.0
Serum albumin	6.3	16.3
Immunoglobulins	20.6	10.9
Lysozyme	1.6	—
Miscellaneous	17.5	12.5

1. From Kunz, C., Lonnerdal, B. Casein micelles and casein subunits in human milk. In: Protein and non-protein nitrogen in human milk. Atkinson, S., and Lonnerda,l B., (eds), CRC Press, Boca Raton, FL, pp 10-24, 1989.
2. 10 mg/l of cow's milk, 30-100 mg/l of sweet whey.

The question for the infant formula manufacturer is, to what degree does infant formula need to be humanized? Plausible answers to this question range from humanizing the whey to casein ratio to the use of modified whey proteins to serve a particular, and sometimes critical, function in infants. Examples of the latter are hydrolyzed whey proteins for cow milk protein allergy and an increased whey to casein ratio to support favorable metabolic balance in premature infants.

COMPOSITIONAL STRATEGY FOR THE USE OF WHEY PROTEIN IN INFANT FORMULAS

The milks of most mammals contain the same general classes of proteins, casein and whey. However, these are functional definitions based on whether the respective proteins precipitate or remain soluble in response to manipulations in milk pH. Whereas, whey proteins are soluble at lower pH, casein proteins are insoluble and precipitate. The species-dependent compositional heterogeneity within these functional classes is most dramatic in whey proteins. While human milk is whey-predominant, cow's milk is casein predominant. The whey to casein ratio of mature human milk is 60:40 and that of cow milk is 18:82 (or 20:80). As a result, some infant formula manufacturers have chosen to enrich their cow's milk-based formula by adding whey protein. This requires the addition of enough whey protein to consist of 42% of the total protein provided by the formula. Approximately 6 g of whey protein would need to be added to 9 g of cow's milk protein in a typical cow's milk-based formula delivering 15 g of protein/l. This strategy has been popular throughout the world and has the advantage of a simple marketing message that can easily be comprehended by parents.

The whey to casein ratio of human milk changes as a function of the stage of lactation; from 90:10 in early lactation, to 60:40 in mature milk and 50:50 in late lactation. Which of the human milk ratios is the correct target for an infant formula manufacturer? After conducting extensive research, the industry has decided that the whey to casein ratio of mature human milk is the most appropriate composition for an infant formula. However, the relative amounts of the whey proteins are dramatically different in human and cow's milk (Table 1). Another approach would be to increase the concentration of alpha-lactalbumin and lactoferrin in cow's milk using fractionation technology. This approach is not currently feasible for most infant formula markets. In the end, the compositional strategy is undermined by species-dependent heterogeneity in whey proteins and technical/cost limitations.

PLASMA AMINO ACID STRATEGY FOR THE USE OF WHEY PROTEINS IN INFANT FORMULAS

One can argue that generations of infants have grown without ill effects on formulas made from unmodified cow's milk. However, taurine, for example, was not included in infant formulas for decades, only to be shown to be essential in the infant. In this context, human milk produces a different plasma essential amino acid profile in the infant than unmodified cow's milk or whey protein infant formulas. Infants are known to be particularly sensitive to alterations in plasma amino acid profiles. Perhaps reflecting this sensitivity, total amino acid requirements of the human infant are much higher than those at other stages of life. These elevated requirements reflect the rapid rate of growth and development of the infant. In this context, it is important to consider that a formula-fed infant consumes all of its protein from a sole source until the introduction of solid foods. This means that formula-fed infants are uniquely susceptible to nutritional insufficiencies, the results of which could be devastating.

Given the widespread use of cow's milk-based infant formula, infants will benefit from improvements that more closely match the plasma essential amino acid profile of the breastfed infant. Amino acids have functions beyond serving as substrate for protein synthesis, including the synthesis of hormones, bile acids, and neurotransmitters. An example of the effect of a dietary amino acid on neurotransmitters and behavior is provided by tryptophan. In studies, sleep latency was reduced in infants fed supplemental tryptophan. Plasma tryptophan concentration was increased and is thought to increase the transport of tryptophan across the blood brain leading to elevated conversion of tryptophan to serotonin and melatonin in the brain, and ultimately leading to changes in sleep behavior. Based on this evidence, the goal of this strategy is to match the plasma amino acid profile of the breastfed infant as closely as possible.

A mathematical equation that yields a single value summarizing the closeness of a formulation to the plasma essential amino acid profile of a breastfed infant has been developed. This data revealed that a formula with a whey to casein ratio of 48:52 yielded a plasma essential amino acid profile closer to that of human milk than either a formula with a 60:40 whey to casein ratio, or a formula with 100% whey protein. Thus, the formula with the 60:40 whey to casein ratio of human milk did not match the human milk plasma essential amino acid profile as well as formulas with less whey. This equation can predict the plasma essential amino acid profile of any protein mixture, as long as the amino acid profiles of the constituent proteins are known.

Premature Infants

The vast majority of formulas marketed for premature infant formulas are whey-predominant with a whey to casein ratio of 60:40. It is thought that casein-predominant formulas lead to excessive plasma concentrations of tyrosine and phenylalanine. In addition, those fed whey-predominant formulas had metabolic responses more similar to those observed in premature infants fed pooled human milk. In order to meet the high protein requirements of premature infants these formulas typically contain a total of 20 to 24 g protein/l.

Older Infants and Children

While the protein requirements per body weight are lower in older infants (6-12 months of age) and young children (1-3 years) compared to younger infants; their daily requirements are higher. Although formula can constitute the sole source of nutrients in older infants, typically these formulations supplement energy and nutrients derived from staple foods. According to the guidelines adopted by Codex Alimentarius Commission, 100 g of the product should contain about 15 g of a high quality protein. Many formulations for this group are made with nonfat milk, commercial formulations are beginning to use supplemental whey protein (Table 2). The intake of essential amino acids should not be limited during this period of very rapid growth. A combination of nonfat milk and whey protein is particularly rich in essential amino acids. In addition, various whey fractions are particularly useful when formulating clear, acid beverages favored by younger children.

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THE USE OF WHEY PROTEINS IN FORMULAS

Traditionally, infant formulas were based on cow's milk which has an inherent whey to casein ratio of 18:82. Today, supplemental whey protein is used worldwide in a variety of infant formulas. The commercial infant formulas shown in Table 2 meet Codex Alimentarius Commission guidelines and are generally supported by quality studies demonstrating good growth and development.

The concentration of whey protein ranges from 48% to 100% of total protein. As discussed later, the relative amounts of milk protein and whey protein can influence formula stability. In addition, as the percentage of protein as whey protein increases, the amount of water soluble vitamins and some minerals (especially calcium) that must be added to the formulation in order to meet Codex guidelines increases. The identity of these minerals and vitamins is determined by multiple variables including whether the whey protein is ultrafiltered or demineralized. These modifications; however, are minor and there are commercial examples of formulas containing a wide range of whey protein concentrations.

Supplemental whey protein is also being used in formulas for older infants and young children. As new health benefits are discovered for various whey fractions and whey-derived peptides, this area will represent an opportunity for the manufacturer to differentiate its products.

Table 2. Representative Infant and Follow-on Formulations Containing Supplemental Whey Protein

Formula Type	Protein Sources	Whey:Casein	g Protein/100 mL
Infant	Whey Protein, SMP[1]	48:52	1.5
Follow-on[2]	SMP	18:82	1.7
Infant	Whey Protein, SMP	60:40	1.4
Follow-on[2]	SMP	18:82	1.7
Infant	Whey Protein, SMP	60:40	1.5
Follow-on[2]	SMP	18:82	
Infant	Whey Protein	100:0	1.6
Follow-on[2]	SMP	18:82	1.7
Follow-on[3]	Whey Protein, skim milk	NA	2.0
Follow-on[3]	Skim milk	18:82	2.8
Follow-on[3]	Skim milk, whey protein	38:62	2.2

1. Skim milk powder
2. Recommended for infants from 6-12 months of age.
3. Recommended for infants older than 6 months and children up to 2 years of age.

Typical Composition of Children Formula and Ingredients Used

Starter and Follow-on Formulas

Nutrient	%/100 g Dry Product	Ingredients Often Used in Commercial Products
Proteins	10–15%	• Skim milk powder and whey protein concentrate • Skim milk powder and demineralized whey
Fats	22–28%	• Vegetable fat blends
Carbohydrates	52–57%	• Lactose • Lactose and maltodextrin • Modified starch, sucrose (growing-up formulas)
Minerals and micronutrients, amino acids	3–5%	• Minerals and micronutrients—various forms and sources. Added amino acids
Vitamins, others	4%	• Vitamins, and in some formulas nucleotides, prebiotics, lactoferrin

There has been an interest in the use of cow's milk whey protein enriched in alpha-lactalbumin due to its high concentration in human milk and its beneficial amino acid profile. In particular, it is hypothesized that an alpha-lactalbumin-enriched whey protein concentrate would facilitate a very close plasma amino acid profile match for human milk. Alpha -lactalbumin has high concentrations of cystine and unusually high concentrations of tryptophan. Increased concentrations of alpha-lactalbumin in protein-reduced cow's milk-based infant formula elevated plasma tryptophan concentration to the same level seen in breast-fed infants. In these studies, protein-reduced formulas were fed to enhance the plasma ratio of tryptophan to the other large neutral amino acids as discussed above. Recent technological advances would likely obviate the requirement for protein reduction in order to see breast-fed plasma concentrations of tryptophan.

While the incidence of allergy to cow's milk protein is low, the symptoms are severe and in some cases life-threatening. The symptoms include vomiting, diarrhea, gastrointestinal disturbances, excessive crying, eczema, loss of weight and even anaphylactic shock. Traditionally, formulas made with extensively hydrolyzed casein have been used to manage infants with severe milk protein allergies. In the 1990's, extensively hydrolyzed whey protein formulas have been found to be an effective treatment in infants and children with cow's milk allergy. These formulas tend to have significant cost, taste and odor advantages over their casein counterparts. In addition, recent evidence suggests that extensively hydrolyzed whey protein formulas are an effective means of treating the symptoms of colic in milk-allergic infants.

Whey Protein Concentrate-based Infant Formula Mix*

Ingredients	Usage level
Whey protein concentrate 34%	18.50%
Skim milk powder	16.00%
Lactose	37.00%
Fat blend	27.00%
Lecithin	0.50%
Vitamins and minerals	1.00%
Water	As needed
Total	100.00%

Procedure:

1. Calculate formula. Add WPC34, skim milk powder and lactose to water. The quantity of water should be that required to produce an easily processed, concentrated liquid.
2. Heat the solution to approximately 60°C and mix in the lecithin, fat blend, vitamins and minerals.
3. Continue heating to pasteurize. Homogenize—two-stage homogenization recommended with pressures of 141 kgf/cm^2 in the first stage and 35kgf/cm^2 in the second.
4. Spray dry and agglomerate for easier reconstitution.
5. To rehydrate, blend 10% dry formula and 90% potable water by weight. Heat to pasteurize, and cool to feeding temperature.

* Please consult a physician or dietitian for use of formulas for infant and child nutrition.

Toddler Formula with Iron* Typical composition. Product designed to meet the needs of older infants (6-18 months)

Nutrients per 100 Calories	
Protein	3-5.5 g
Fat	5.49 g
Carbohydrate	10.56 g
Linoleic acid	1,000 mg
Vitamin A	300 IU
Vitamin D	60 IU
Vitamin E	3 IU
Vitamin K	8 mcg
Vitamin B1, B2	150 mcg
Vitamin B6	60 mcg
Vitamin B12	0.25 mcg
Niacin	1,050 mcg
Folic acid (folacin)	15 mcg
Pantothenic acid	450 mcg
Biotin	4.4 mcg
Vitamin C	9 mg
Inositol	4.7 mg
Calcium	118 mg
Phosphorus	64 mg
Magnesium	6 mg
Iron	1.8 mg
Zinc	0.75 mg
Manganese	5 mcg
Copper	90 mcg
Iodine	6 mcg
Sodium	24 mg
Potassium	105 mg
Chloride	65 mg

Ingredients: Skim milk, lactose, high-oleic safflower oil, coconut oil, soy oil, ***whey protein concentrate****, minerals, vitamins and other nutrients.*

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Lactoferrin

In recent years it has become clear that certain dietary proteins and peptides have specific biological activities. Protein fractions such as lactoferrin have been identified that have bioactive properties at low concentration. Lactoferrin is a protein with a number of exciting functional properties, and it is already used in many commercial products such as infant formulas, sports and functional foods, veterinary and feed specialties and personal care items such as mouthwash and toothpaste. Lactoferrin has antibacterial and antioxidant properties and is a major nonspecific disease resistance factor found in the mammary gland. It probably mediates protection against microbial infection of the mammary gland. Lactoferrin sequesters and solubilizes iron, thus controlling the amount of iron in metabolism. Although isolated about 30 years ago, the precise biological roles of lactoferrin are still emerging. Bovine lactoferrin is highly homologous to other lactoferrins and transferrins. In general, the properties of lactoferrin include antibacterial and antiviral properties, prevention of the growth of pathogenic organisms in the gut, stimulation of the immune system, regulation of iron metabolism and control of cell or tissue damage.

Some of the interest in infant formula applications originates from the comparison of human milk to bovine milk. Lactoferrin concentration in human milk is 0.20 g/100 ml vs. 0.01 g/100 ml in mature cow's milk. Lactoferrin is available as a commercial ingredient and is used by infant formula manufacturers in several countries to enrich their formulations.

Adapted from Dr. German, J.B. et al. Personal communication. May 2000.

Whey Proteins in Medical Nutritional Products

Considerations for using proteins in infant formula and medical nutritional products include:

- Nutritional issues: digestibility, amino acid content and tolerance by the infant.
- Bioactivity: hormonal, anti-infective, transporter, hydrolysis-resistant peptides.
- Functionality.
- Availability and cost.

From a manufacturer's perspective, product stability issues are also important. They concern:

- Physical deterioration of liquid infant formula and medical nutritional products over the shelf-life of the product.
- Creaming: rise of fat globule.
- Sedimentation: settling of insoluble proteins or mineral salts.
- Gelation: loose binding of proteins and/or hydrocolloids.
- Serum separation: syneresis that occurs with increases in gelation and creaming.
- Graininess: protein aggregation.
- Some aspects of whey protein manufacturer can affect product stability. They include raw milk pretreatment, cheese type, heat treatments and, when applicable, type of demineralization process.

Infant formula and medical nutritional product stability is influenced by:

- Formula composition: the levels of di-and polyvalent ions, buffer salts (citrates, phosphates) and the presence of emulsifiers and stabilizers.
- Processing, to include homogenization temperature and pressure.

The advantages to using whey proteins in medical nutritional products include: a cleaner flavor, improved amino-acid pattern, improved physical stability, availability of low lactose hydrolysate, anti-oxidant qualities and the creation of a slight gel that can help suspend cocoa powder, for example, in flavored products.

FUNCTIONAL PROPERTIES OF WHEY PROTEINS

The functional properties of whey proteins include those that permit their use for emulsification, gelation, water binding, solubilization, whipping/foaming and viscosity development, as has been extensively reviewed. Greater functionality translates in food applications, not only in their relative ability to provide particular physical properties to foods, but in the reproducibility of these properties and in their ability to provide more than one functional purpose in a food application. The various three-dimensional folded structures of whey proteins are responsible for their conformation and functionality. Various external factors also influence the functional properties of whey protein concentrates, including concentration, state of the whey protein, pH, ionic environment, preheat and heat treatments and the presence of lipids. Whey protein isolates and whey protein concentrates are valuable as food ingredients not only for their ability to aggregate and to provide structure to foods but because they are highly soluble over a wide pH range. This property makes them suitable for use in such applications as sports beverages and liquid meal replacements. As emulsifiers, concentrated whey proteins find wide applications in the formulation of nutritional protein drinks and other medical nutritional products.

The mammalian infant is conspicuous for its immature development at birth. Humans especially, are born with organs and tissues in a formative state, and the provision of specific factors that support development is clearly an activity of milk. Whey proteins are again conspicuous for their ability to support development in both in vitro models and in vivo studies. Applications of such activities and concentrated factors would be a logical strategy for food products in which supporting development is a desired outcome. Recovery of tissues post-trauma and injury are the most obvious examples.

It has been speculated, although the results are not yet clear, that whey proteins provide a significant benefit to recovery of tissues when the stress is not serious damage or trauma, such as the stress associated with exercise. Nevertheless, the mechanisms of action known for various factors in whey are consistent with such benefits.

The substantial body of knowledge emerging on the antimicrobial properties of whey proteins such as lactoferrin have brought this benefit of milk components even beyond the scientific community to general acceptance by a large lay audience. An apparent evolutionary benefit of milk has been to promote, through a variety of mechanisms, a microfloral population with many protective properties. The value of whey components as prebiotics in stimulating a beneficial microflora is not as well established to date, yet this awareness is continuing to develop. The value of whey components in protection is a nutritional benefit that is directly transferable to all life stages.

High Protein Cookies

Ingredients	Usage level
WPC80[1]	**18.30%**
Cake flour	18.25%
Brown sugar	21.35%
Butter	13.35%
Skim milk powder	1.30%
Chocolate chips[2]	17.35%
Eggs	2.55%
Vanilla extract	0.30%
Salt	0.25%
Sodium bicarbonate	0.25%
Water	6.75%
Total	100.00%

Nutrition Information:

Serving Size:	1 cookie/30 g
Nutrients per serving:	
Calories	120
Fat	5 g
Cholesterol	20 mg
Sodium	85 mg
Carbohydrates	14 g
Protein	6 g
Calcium	4% (of Daily Value)

Procedure:

1. Mix butter, brown sugar and NDM at medium speed for two minutes.
2. Add eggs, vanilla and water; mix for another minute.
3. Blend in flour, WPC, salt and sodium bicarbonate.
4. Fold in chocolate chips.
5. Drop 30-gram dough portions onto cookie sheet.
6. Bake at 175°C for 10 to 12 minutes.
7. Cool.

Developed by California Dairy Ingredients Applications Lab, San Luis Obispo, CA

Fruit Smoothie

Ingredients	Usage level
Seedless strawberry puree (7 Brix)	48.50%
Water	20.00%
Liquid fructose	12.00%
Seedless banana puree (22 Brix)	8.00%
WPC80[1]	**7.00%**
42 DE corn syrup	4.00%
Milk calcium	0.40%
Citric acid	0.10%
Total	100.00%

Nutrition Information:

Serving Size:	120 g
Nutrients per serving:	
Calories	120
Fat	0 g
Carbohydrates	21 g
Protein	7g
Calcium	15% (of Daily Value)

Procedure:

1. Mix the WPC, milk calcium and water until hydrated.
2. Add the fructose, corn syrup, and citric acid.
3. Mix in the strawberry and banana puree.
4. Freeze in soft serve/slush machine.

Developed by the Wisconsin Center for Dairy Research Madison, WI

Protein-fortified Fruit Beverage

Ingredients	Usage level
Water	80.00%
Fructose	9.98%
WPC80[1]	**6.26%**
Corn syrup solids	2.25%
Citric acid	0.78%
Milk calcium	0.59%
Raspberry flavor	0.13%
Red color #40	0.01%
Total	100.00%

Procedure:

1. Blend all dry ingredients well.
2. Disperse one bag (32 oz or 908 g) of dry mix in (3.8 l) water, stirring or shaking until fully hydrated.
3. Finished pH is about 4.0.
4. Cold-fill bottles and pasteurize to 88°C.

Developed by the Wisconsin Center for Dairy Research Madison, WI

[1] Whey protein concentrate 80%

[2] Other inclusions can be substituted: compound coatings, dried fruits, other.

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Published by U.S. Dairy Export Council®
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