

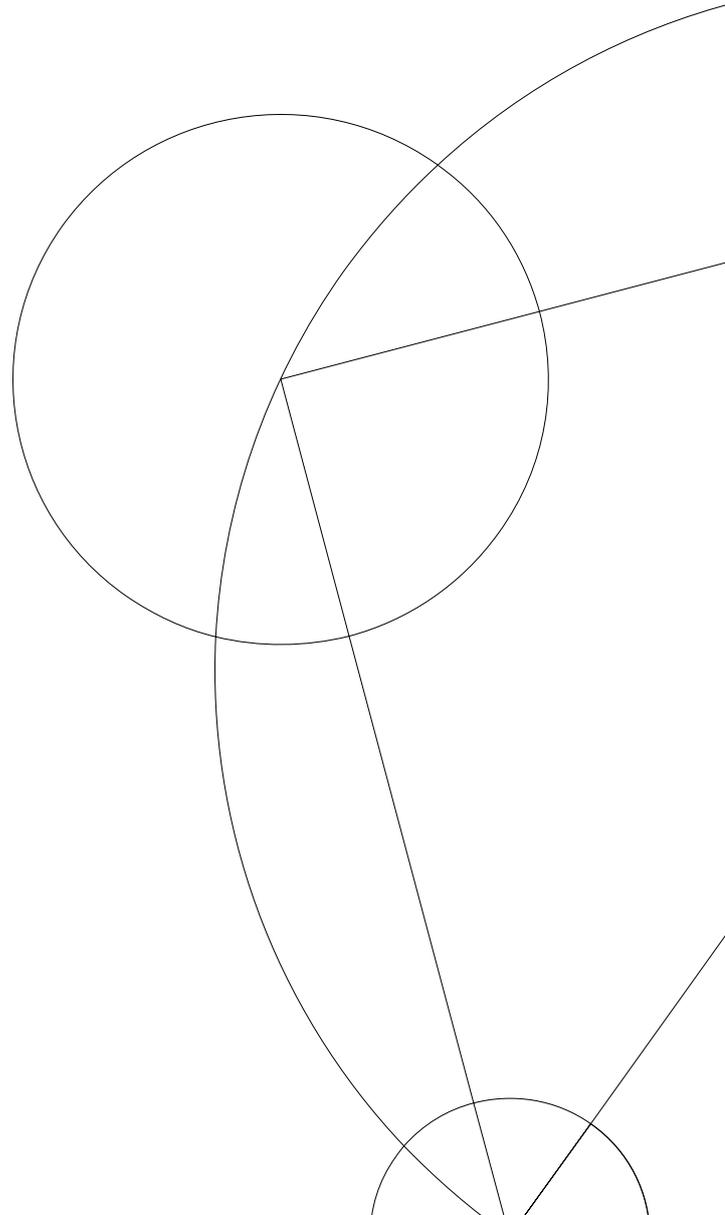


Evaluation of whey permeate in the treatment of moderate malnutrition

Department of Human Nutrition



Prepared by Benedikte Grenov,
Anne-Louise Hother Nielsen,
Christian Mølgaard and Kim
Fleischer Michaelsen for Arla
Foods Ingredients Group P/S



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Abbreviations

Abbreviation	Explanation
ADG	Average daily gain (feeding trials)
ADFI	Average daily feed intake (feeding trials)
CSB	Corn soya blend
CSB++	Corn soya blend plus-plus (super cereal plus)
FBF	Fortified blended food
HEB	High Energy Biscuits
PDCAAS	Protein digestibility-corrected amino acid score
RUSF	Ready-to-use-supplementary-food
RUTF	Ready-to-use-therapeutic-food
SCFA	Short-chained-fatty-acid
SMP	Skimmed milk powder
WFP	World Food Programme
WP	Whey powder
WPC	Whey protein concentrate (typically contains 34% or 80% whey protein)
WPI	Whey protein isolate (> 90% whey protein)
WSB	Wheat soya blend

Summary

Whey is the liquid part of milk that remains after coagulation of cheese curd. After removal of whey proteins by ultrafiltration (and nanofiltration) the remaining whey permeate is concentrated and spray dried. Variolac is the brand name of whey permeate manufactured by Arla Food Ingredients. It contains minimum 85% lactose, maximum 3 % nitrogen containing compounds and approximately 0.6 % calcium, 0.6 % phosphorus, 1.6 % potassium, 0.1 % magnesium, 0.6 % sodium and 1.0 % chloride.

Milk and milk powder is considered a valuable, however expensive component in the treatment of malnutrition. This report evaluates the potential use of whey permeate in the treatment of moderately malnourished children.

The mineral package of permeate contains mainly type II growth minerals and calcium. Overall the amount of these minerals as well as the relative nutrient:nutrient ratios in permeate are considered relevant for incorporation in food for moderately malnourished children as long as the recommendations for daily nutrient intake in this population are taken into account.

Breast milk is considered to be the optimum source of nutrients for infants and young children. It contains approx. 7 % of lactose compared to 4.6% in cow's milk. Lactose has been shown to have a growth promoting effect in weanling piglets and a beneficial prebiotic effect leading to increased growth of lactobacilli and bifidobacteria in the colon. In humans a prebiotic effect of lactose has been observed in adults with lactase deficiency and is indicated in premature infants with immature lactase activity as well as in term infants. Lactose may have a similar prebiotic effect in malnourished children with secondary lactose deficiency. Adding lactose to food for moderately malnourished children would increase the energy density and likely improve the palatability of food aid. Compared to sucrose which is currently used to increase energy density in some food aid products, lactose has a lower cariogenicity. Finally lactose may enhance mineral absorption in infants and young children.

Lactose malabsorption or intolerance does not seem to be a major problem in rehabilitation of moderately malnourished children below 5 years.

Permeate could be added as an ingredient to existing types of food supplements for moderately malnourished children. This includes among others fortified blended foods, ready-to-use-food and

high energy biscuits. The amount should be balanced not to dilute nutrient content of other ingredients too much and not to reach upper limits for the intake of lactose and minerals, especially sodium.

Overall permeate could be used in food aid for moderately malnourished children mainly as a “natural carbohydrate source”. This would increase the energy density and possibly the palatability of the food, have a reduced cariogenic activity compared to sucrose and potentially have a prebiotic effect.

Studies are needed to identify relevant doses in malnourished infants where the taste, potential prebiotic activity and risk of osmotic diarrhea and growth are evaluated.

Further studies could be made to investigate the cariogenic activity of food aid with lactose compared to sucrose in malnourished children.

Background

Whey Permeate

Whey is the liquid part of milk that remains after coagulation of cheese curd. Liquid whey has been used for animal feed for decades. Milk was transported to the dairy and whey was transported back to the farmers to feed calves or piglets during weaning. Today, whey is not regarded as a low value by-product but is processed into different milk powders for different applications and with different nutritional and technological properties. These products include dried whey (eg. sweet whey powder containing approx. 12% protein), whey protein concentrates (WPC34, WPC80 with 34% and 80% whey protein) and whey protein isolate (WPI90 with > 90% whey protein), pure lactose and finally whey permeate which is the remaining parts of whey after removal of whey proteins.

Variolac is the brand name of whey permeate produced by Arla Food Ingredients. After ultrafiltration and nanofiltration where whey proteins are removed, the whey permeate is concentrated and spray dried in a process that results in free flowing powder.

Moderate malnutrition and milk

According to a large coordinated global effort to evaluate the status of malnutrition in low-income countries which is published in an often cited series in the Lancet (1,2), 178 million children corresponding to approximately 1/3 of children living in low-income countries are stunted*, 55 million children are wasted** and 19 million children are severely wasted** and approximately 35% of child mortality under five years is estimated to be attributed to malnutrition either as a direct cause or an indirect consequence of malnutrition.

Breast milk is considered the optimum source of infant nutrition. It has a high level of lactose and a low level of protein and fat compared to cow's milk. The importance of breast milk also applies to moderately malnourished children and promotion of breast feeding has been shown to be one of the most important ways to fight malnutrition (2). Any complementary feeding should aim at supplementing and not replacing breast milk.

*Stunting: height for age is reduced by at least 2 standard deviations compared to the WHO growth standards.

** Wasting, severe wasting: Height for weight is reduced by 2 or 3 standard deviations, respectively, compared to the WHO standard growth curves

Milk (cow's milk unless otherwise stated) is an important ingredient in the treatment of undernutrition. Together with meat and other animal source products, milk provides a range of essential nutrients, which are present in a low concentration or has a low bioavailability in a vegetable based diet. A typical vegetable based diet often consists of one staple (eg. maize, rice), with supplementation of a few vegetables, legumes, pulses and fruit, which is consumed by populations with a high prevalence of undernutrition.

Over many years, evidence has been collected overall supporting the findings that milk stimulates linear growth (3). It is likely that milk consumption stimulates IGF-1 (insulin-like growth factor -1) and thereby induces linear growth. Many of the intervention studies supporting the linear growth effect have been conducted in malnourished populations but also intervention studies as well as observational studies in high income countries have resulted in increased linear growth in response to higher consumption of milk.

Milk is an excellent source of many nutrients. Milk protein has gained special interest as it contains all the essential amino acids and the protein quality index, PDCAAS (Protein digestibility-corrected amino acid score), is very high, 120%, compared to 65% for corn soya blend and 35% for corn meal (4). The main protein fractions of milk are casein and whey, which account for approx. 80% and 20%, respectively (5). Other important milk nutrients include calcium, phosphorus, magnesium, zinc and several B-vitamins and bioactive factors (milk peptides etc.).

Large, randomized, controlled intervention studies have shown that newer products used to treat moderate malnutrition like ready-to-use-supplementary-food (RUSF) containing 30% milk powder (SMP or WP) and a new version of fortified corn soya blend, CSB++, containing 8% of SMP result in high recovery rates and significant improvements in anthropometric measurements (6,7).

There is however no firm results regarding the minimum amount of milk that would have a positive effect on growth and rehabilitation of malnourished children and the effects of different fractions of milk are not clear.

Price is a limiting factor when it comes to addition of milk powders to food aid. Milk powders are expensive and prices fluctuate significantly (4). In order to be able to treat as many undernourished children as possible, it is therefore important to investigate how to find cheaper food solutions.

Whey permeate is a relatively cheap by-product from cheese and whey protein concentrate (WPC) manufacturing and has a stable price compared to both skimmed milk powder (SMP) and WP/WPC. Below the potential of using Variolac from Arla Foods Ingredients in the treatment of moderate malnutrition is described and discussed.

Variolac may also be useful in the treatment of severe acute malnutrition. This would require changes to the WHO treatment guidelines for inpatient and outpatient treatment of severely acutely malnourished children. These guidelines are implemented by many low income countries and changing them may be a lengthy process which could possibly take several years.

Description of Variolac

The composition of whey permeate varies depending on the type of cheese and manufacturing conditions. Variolac is produced at a whey protein plant sourcing whey from cheese plants in Argentina. The composition is quite uniform and can be seen in table 1 below.

Chemical specifications		Minerals (typical values)	
Protein (Nx6.38)*	Max 3%	Sodium	0.6 %
Lactose monohydrate	Min 85%	Magnesium	0.1 %
Ash	Max 7%	Phosphorus	0.6 %
Moisture	Max 3.5%	Chloride	1.0 %
Energy (kJ/100 g)	1.480	Potassium	1.6 %
		Calcium	0.6 %

Table 1. Composition of Variolac

*Permeate only contains trace amounts of protein. Nitrogen found in permeate includes urea, creatine creatinine, uric acid, orotic acid and ammonia. The amount of “protein” is calculated as the total amount of nitrogen multiplied by 6.38 (8).

Variolac has a storage stability of 12 months at max. 25 – 30°C and 65% relative humidity, but the shelf life may be extended up to 24 months.

Variolac is a free flowing powder.

Lactose

Lactose is the most abundant carbohydrate of mammalian milk and milk is the only known natural source of significant amounts of lactose. Human milk contains approx. 7 % of lactose and cow’s

milk contains approx. 4.6% of lactose. In exclusively breast fed infants lactose constitutes about 40% of the daily energy consumption.

From a biological perspective lactose should therefore be a good energy source for infants and young children. Below some of the potential advantages and disadvantages of lactose in relation to treatment of moderately malnourished children are discussed.

Prebiotic effect of lactose

Lactose is hydrolyzed to glucose and galactose in the presence of lactase and absorbed in the small intestine. If the lactase activity in the small intestine is not sufficient to hydrolyze all ingested lactose, the residual lactose enters the colon where it is fermented by the colonic microbiota (8).

In healthy adult lactose maldigesters, lactose has been shown to increase the growth of lactobacilli and bifidobacteria (9, 10).

In newborn infants, human milk is considered to have a high impact on microbial colonization. Breastfed infants have a predominance of bifidobacteria and lactobacilli, whereas formula fed infants develop a mixed microbiota with a lower number of bifidobacteria. The “bifidogenic effect” of human milk is related to a complex of interacting factors, including the prebiotic effect of lactose and human milk oligosaccharides (11). In preterm infants it has been estimated that 50% - 70% of the ingested lactose might pass into the colon and in term infants lactose is probably not fully digested (12).

New methods are used to follow the exact degradation of food components in the gastrointestinal tract and how it affects the gut microbiota. In a recent study performed in an artificial computer controlled dynamic model of the large intestine, ¹³C-lactose was fed into the model which had been inoculated with the gut microbiota of a healthy, lactose fermenting individual. It was shown that ¹³C-lactose was almost exclusively fermented by members of the actinobacteria group, of which bifidobacteria constituted 97% and the major bifidobacterium species fermenting lactose was *B. adolescentis* (8).

When lactose and other carbohydrates are fermented in the colon, lactate, short-chain fatty acids (SCFAs) and gas are produced (8, 13). The SCFAs mainly include acetate, propionate and butyrate. The SCFAs are important to maintain homeostasis in the body and each SCFA has several functions

in different body tissues, eg butyrate serves as an important fuel for colonocytes (8, 13). The profile of SCFAs produced depends among others on the microbiota and available carbohydrates. A number of health beneficial effects have been associated with prebiotics including increased mineral absorption, laxation, potential anti-cancer properties, lipid metabolism, anti-inflammatory and other immune effects. Many of these effects can be linked to SCFAs produced after fermentation of the prebiotics (13).

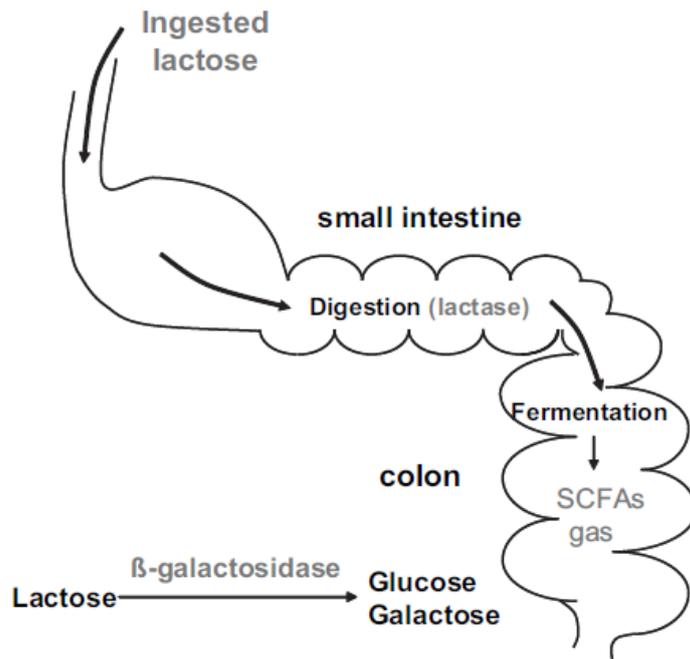


Figure 1. Fate of lactose in the gastrointestinal tract (8).

Due to the beneficial prebiotic effects of lactose, it has been speculated that the large population of lactase-deficient individuals should not avoid lactose completely but rather consume smaller amounts to obtain the beneficial effects (14). It is also recommended that in preterm infants with an immature intestinal tract and low production of lactase, lactose should constitute between 40% and 100% of carbohydrate intake (12).

It has been shown that long-term ingestion of lactose lead to diminished intolerance as measured by the breath hydrogen test. This adaptation may be due to changes in the colonic microbiota (14).

Lactose intolerance

Most mammals normally become lactose intolerant after weaning (primary lactase deficiency), but some human populations have developed lactase persistence. In this case lactase production continues into adulthood (15, 16).

Lactose maldigestion and intolerance usually develop at 3 – 5 years of age and is estimated to affect approx. 75% of the global population (5). The symptoms of lactose intolerance are mainly flatulence, abdominal pain, bloating and diarrhea (17). The type and severity of the symptoms depend on a range of conditions including the dose of ingested lactose, residual lactase activity, gastric emptying rate, intestinal transit time, presence of other food components together with lactose and the composition and metabolic activity of the colonic microbiota fermenting lactose as well as psychological factors regarding perception of abdominal pain and discomfort (8, 14, 17).

Most lactase malabsorbers are able to tolerate some lactose. According to available evidence, adults and adolescents can ingest 12 g of lactose in a single dose (equivalent to 1 cup of milk) with no or minimal symptoms and larger amounts if ingested with meals throughout the day. (17)

Lactase is present predominantly along the brush border membrane of the differentiated enterocytes lining the villi of the small intestine (15, 16). Diarrhea, intestinal diseases and enteropathy may disrupt the intestinal barrier and cause transient lactose intolerance (secondary lactase deficiency).

Malnourished children often have frequent episodes of diarrhea due to reduced immune function and high exposure to enteropathogens. This leads to disruption of the intestinal barrier, including villus atrophy and crypt hyperplasia and transient (secondary) lactase deficiency may occur (18).

In a recent study, it was concluded that lactose intolerance affected 25.5 % of severely malnourished children presenting to a hospital nutrition unit with diarrhea (19). Children with kwashiorkor were affected more often than children with marasmic-kwashiorkor or marasmus. The diagnostic methods used in this study were not the golden standard lactose hydrogen breath test, but simpler and less specific methods evaluating stool reducing substances and fecal pH as indicators of presence of sugar and lactic acid in the faeces, respectively. The study recommended screening for lactose intolerance and to consider using lactose-free diets and yoghurt in children with lactose intolerance and poor response to standard therapeutic milk formula. The authors did not discuss the duration of lactose-free diets.

The effect of lactose malabsorption on growth and recovery was studied in 20 severely malnourished male children between 15 – 36 months (20). Ten children received a standard milk based formula and 10 children matched as closely as possible with respect to age, clinical severity, degree of edema, estimated weight for height, serum protein concentrations and history of diarrhea received the same formula treated with β -galactosidase ensuring at least 90% hydrolysis of lactose. The group receiving the standard milk based formula developed more diarrhea compared to the group receiving the lactose reduced formula, but recovery and growth rates were satisfactory and reaching the same levels in both groups.

A Gambian study (21) enrolled 113 rural breastfed 2 – 15 month old infants for an average of 7.5 months. Lactose maldigestion was estimated monthly by measurement of urinary lactose and lactulose after a dose of lactulose 1 – 2 hours after a full breast-feed. By assuming constant intake of lactose (2 g/hour) and by using lactose excretion in urine as an indicator of low lactase activity, the study showed that intestinal permeability and lactose malabsorption both increased with age. Up to 6 months the results of urinary lactose:lactulose was considered in the normal range, but after this age the relative excretion of lactose:lactulose indicated lactose malabsorption, which increased with age. Lactose malabsorption was related to poor growth (weight and length). Enteropathy measured as increased intestinal permeability accounted for the major negative impact on growth, but lactose malabsorption contributed to negative growth by 30% of the total effect. The study concluded that even though lactose malabsorption did occur in breast-fed Gambian infants, breast feeding should continue as the nutritional and immunological benefits of breast milk outweigh any disadvantages.

Brewster (22) (Prof. at School of Medicine, University of Botswana) recommends adjustment of the WHO protocol for treatment of severely malnourished inpatients as high mortality rates are still observed in many African hospitals. One of his recommendations is to use low lactose, low osmolality milk for treatment of severely malnourished inpatients during the early treatment stage at hospital admission. The background for his recommendation is frequent findings of severe lactose and monosaccharide intolerance in HIV infected children with diarrhea and children with environmental enteropathy and positive results obtained with lactose-free, low-osmolality milk formula in children with acute diarrhea and/or malnutrition (Z -score (weight for age) < -2 SD) (23).

Current WHO recommendations for severely acutely malnourished children include frequent small meals with therapeutic milk, F-75 and F-100 or Ready-to-Use-Therapeutic-Food (RUTF) (24, 25).

These products contain 1.25 % of lactose (F-75), 4% of lactose (F-100) and 15% of lactose (RUTF), respectively compared to 7% of lactose in breast milk. As the energy density of RUTF is very high, the total amount of lactose consumed per day is at the level of or lower than the amount of lactose consumed during feeding with F-100.

Breast milk, which contains considerably more lactose than cow's milk, is always regarded as the optimal food for infants also when they have diarrhea as the beneficial nutritional and immunological effects outweighs any potential disadvantages during transient lactase deficiency.

In conclusion we have evaluated that for the majority of malnourished children between 6 months and 5 years of age, lactose intolerance is generally not regarded as a significant challenge and lactose can be included in the diet.

In vulnerable patients like severely malnourished inpatients with HIV and diarrhea it may be necessary to reduce lactose temporarily during early treatment. Further investigations are needed to evaluate if and for how long lactose should be restricted or omitted in these vulnerable patients.

Breastfeeding is encouraged for all children.

Lactose and energy density

Lactose has an energy density of 3.9 kcal/g, which is similar to other carbohydrates, including starch. When starch is cooked it binds water and the resulting porridge or gruel has a considerably lower energy density than the ingredients it was made from. Porridge or gruel given to infants typically have energy densities between 0.6 kcal/g – 0.8 kcal/g, but the density may be as low as 0.25 kcal/g if the food is based on only cereal and water (5). Porridge is therefore a “bulky food”. Studies have shown that the energy intake of children is influenced by the energy density of the food as well as the frequency of meals. If high energy-dense food is supplied, children eat smaller amounts but they do not compensate fully for the extra energy and eat more calories per day. It is proposed that diets for moderately malnourished children between 6 months and 5 years should have an energy density between 1.5 and 2.0 kcal/g (5). Although fat has a considerably higher energy density than carbohydrate (approx. 9 kcal/g compared to approx. 4 kcal/g), sugar is used in products for moderately malnourished children to increase energy density as well as the palatability/taste of the products. RUSF contains up to 30% sugar and CSB ++ contains 9% sugar.

If lactose is added to porridge, fortified blended foods or food supplements, it will increase the energy density of the food.

As lactose does not contain any essential nutrients, the relative amount of nutrients is diluted when lactose is added to a food matrix. If nutrients – or specific nutrients - are scarce or the consumer is eating only small amounts of food due to low appetite or low access to food, it is important that the food contains a balanced and sufficient amount of nutrients.

In relation to food aid this means that addition of lactose necessitates adjustment of other macro and micro-nutrients to meet the daily needs of undernourished populations. If the relative nutrient composition is un-balanced, malnourished children may acquire nutrient deficiencies, may not be able to maintain normal growth and any excess energy, which cannot be used for building lean body mass due to lack of growth nutrients, will then be deposited as fat (26). Although the mechanisms and the causalities are not clear, it seems that there is an increased risk for cardiovascular disease and type 2 diabetes in individuals which have experienced malnutrition during their childhood (27).

Permeate and food palatability

Permeate powder is used in many products to add a “milky taste” and to adjust sweetness of different products.

Young children have an innate sensory pleasure from sweet taste and prefer a more intensely sweet taste compared to adolescents and adults (28). This may reflect the fact that the energy and nutrient needs are higher during growth.

In general the sensation of sweetness is context dependent (29, 30). This means that infants learn what should and what should not taste sweet. In relation to food aid, adding sweetening sugars is likely to favor the taste and intake of the products. Children exposed to food aid containing either sucrose and/or lactose could learn to like them with the level of sweetness they have been manufactured and recognize and develop preference for the products. The risk to develop taste preference for sweet products later in life seems to be low (28).

The content of minerals and salt in permeate as well as the extra minerals and vitamins in food aid may affect the overall taste, and this needs to be tested for further clarification.

Lactose and dental health

The prevalence of dental caries is relatively low in most low-income countries and more than 90% of caries are untreated (31), but the prevalence of caries is high in the primary dentition (the first set of teeth in young children) in developing countries. Periodontal diseases are more prevalent and occur in more severe forms in developing countries, compared to developed countries. This is presumed to be associated with poor mouth hygiene (32).

Numerous epidemiological studies have shown that the level of dental caries and sugar consumption is strongly correlated (31). The frequency of sugar intake as well as the total amount of sugar consumed is important in relation to development of dental caries. The effect of sugar on dental caries is more pronounced with older dental plaques. This may explain why people with poor mouth hygiene are more prone to develop dental caries if they consume high amounts of sugar (33).

Malnutrition has been shown to aggravate dental health problems. Malnutrition has been associated with caries in primary teeth in young children (34) and to some extent also in permanent teeth (35). Protein-energy malnutrition, vitamin D and vitamin A deficiencies have been associated with enamel hypoplasia and salivary gland atrophy (31, 34) and the volume, the antibacterial and physicochemical properties of saliva is compromised in malnourished humans (32, 34).

Addition of sugar to foods for malnutrition for prolonged periods of time may not be appropriate when considering the risk of dental caries and dental health. The amount of sugar in some RUTFs is approx. 28% - and with 2 – 3 sachets of 92 g per child per day, this equals 50 – 80 gram of sucrose per day per child. This amount of sugar increases the risk of dental caries and exceeds the 10 E% recommended by WHO for added sugars in food (31). In addition malnourished children are assumed to have poor mouth hygiene and with frequent exposure to meals containing sugar (it is recommended that malnourished children have frequent small meals) this further discourage addition of large amounts of sugar to food aid.

The only mono- or disaccharide with a reduced detrimental dental effect is lactose (31, 33, 36). Measurement of plaque pH *in situ* after rinsing the mouth with different types of carbohydrates can be seen from the figure below

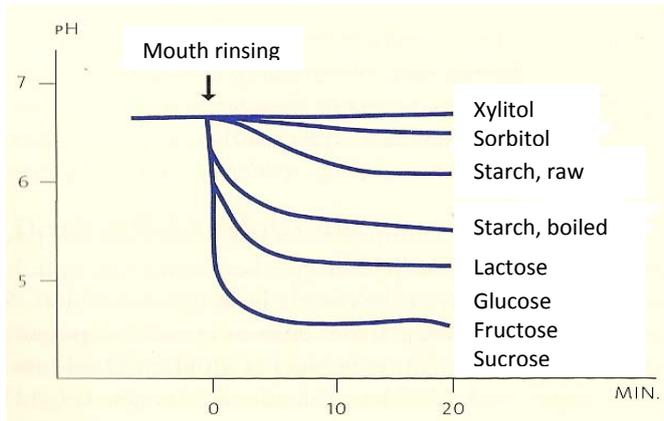


Figure 2 Modified after Neff (37)

A steep and sustained pH drop is increasing the risk of caries and it is generally assumed that hard tooth tissue dissolves when dental plaque pH drops below pH 5.5 (33). Rat studies have confirmed that consumption of human milk or cow's milk has a markedly lower detrimental effect on teeth compared to other sweet liquids (36).

As seen from figure 3, starches have a low risk to develop dental caries and cooked starch is about $\frac{1}{3}$ to $\frac{1}{2}$ as cariogenic as sucrose (31).

Mineral package of whey permeate

The processing of milk to whey and whey permeate changes the absolute and relative composition of minerals present. Whole milk is a good source of calcium, magnesium, phosphorus, potassium, selenium and zinc. A great proportion of the calcium, magnesium and phosphorus present in milk are however bound to the casein fraction of milk, and the mineral content in whey and whey permeate is therefore lower than in whole milk. Other minerals are present as diffusible salts in whole milk and are transferred to whey permeate without any major changes. Potassium, sodium and chloride are almost entirely present as diffusible salts in whole milk and are transferred to permeate. In **Table 2** the mineral content of permeate is compared to the content in skimmed milk powder – which is currently used in a range of food products for moderately malnourished children.

Composition of Variolac compared to Skimmed Milk Powder

Table 2 Type II nutrients + calcium content of whey permeate powder relative to skimmed milk powder.

Nutrient	Gravimetric unit	Per 100 g			Per 100 g lactose		
		Whey permeate ^{ab}	SMP ^c	content in permeate relative to SMP (%)	Whey permeate ^{ab}	SMP ^c	content in permeate relative to SMP (%)
		Energy	kcal	353,7	365	97	398,2
Lactose	g	88,8	50,8	175	100,0	100,0	100
Type II							
Protein	g	2,1	36,2	6	2,3	71,3	3
Sodium	mg	575,0	435	132	647,2	856,3	76
Potassium	mg	1715,0	1596	107	1930,4	3141,7	61
Magnesium	mg	121,5	110	110	136,8	216,5	63
Phosphorus	mg	636,5	956	67	716,5	1881,9	38
Zinc	mg	0,1	4,7	2	0,1	9,3	1
Calcium	mg	554,0	1226	45	623,6	2413,4	26

^aVariolac® 850 is a spray-dried free flowing whey permeate powder

^bData from product information (Batch no 5A29701, produced 27-07-2010 from Arla Foods Ingredients) and Quaterly test analysis provided by Eurofins (14.10.2010)

^c foodcomp.dk

As seen from the table permeate contains a considerable amount of many of the milk minerals important for growth of the young or moderately malnourished child. Compared to SMP, permeate has similar energy content and contains a comparable amount of sodium, potassium, magnesium, and a reduced amount of phosphorus and calcium, whereas the content of protein and zinc is very low. As permeate mainly consists of lactose the mineral content per 100 g of lactose in permeate relative to skimmed milk powder is also shown in the table above.

The bioavailability of minerals from milk is generally considered to be high. Due to the process by which permeate is produced, the minerals must be expected mainly to be present in a soluble, not protein bound form, which might influence the bioavailability of the minerals, e.g. the bioavailability of phosphorus is reduced when bound to casein.

In diets for moderately malnourished children attention should be paid to the sodium content. An upper limit has been set at 550 mmol/1000 kcal for the sodium content of diets for these children (26). Most moderately malnourished children could probably tolerate a higher level, but this level is set to be precautionous as severely undernourished children have increased intracellular and total body sodium associated with a risk of acute heart failure during recovery from malnutrition. For

comparison, the sodium content of F-100 and RUTF which are used for treatment of severely malnourished children is 434 mmol/1000 kcal (26).

The sodium content and the ratio of sodium to potassium of permeate and skimmed milk powder is comparable and must be considered to be at an acceptable level.

Overall the amount of these minerals as well as the relative nutrient:nutrient ratios in permeate are considered relevant for incorporation in food for moderately malnourished children when the above mentioned limitations are taken into account.

Other potential health beneficial effects and components of permeate

Synergistic effect of lactose and minerals

Lactose may enhance calcium absorption and calcium retention in infants (38, 39). Investigation of the influence of lactose on calcium absorption in preterm infants, term infants and adults varies between studies and a firm conclusion has not been reached (12, 40). Enhanced absorption of other minerals including magnesium, manganese and zinc have also been described (38, 41).

Oligosaccharides

Human milk contains significant amounts of human milk oligosaccharides. After lactose and lipids, oligosaccharides are the third most abundant component of human milk with 12 – 14 g/L (42). The content of oligosaccharides in cow's milk is only about 1/20 of the content in human milk.

Sialyloligosaccharides are found in both human milk and cow's milk and a study investigating oligosaccharides from gorgonzola whey permeate found that 7 out of 15 identified oligosaccharides from bovine milk was identical to the composition of human milk oligosaccharides (42). The concentration of oligosaccharides in bovine milk or permeate may be too low to exert an effect in humans.

Bioactive milk peptides

Milk peptides are categorized as “bioactive substances” which are not considered nutrients by definition, but are components with beneficial health effects. They contain a high amount of bioactive milk peptides including β -lactoglobulin, α -lactalbumin, lactoferrin and immunoglobulins (5). However their molecular weights are all above the 10 kDa cut-off value for dairy ultrafiltration.

Therefore only small peptides remain in whey permeate. We did not find any described health effects of these smaller peptides.

Animal studies with lactose/permeate

The digestive system of the pig has been used and recognized as a model for the human digestive tract. Below different types of pig studies are referred indicating different aspects of the relevance of permeate in relation to nutrition of malnourished children.

Growth studies

Sow's milk contains easily digestible protein, lactose and fat. The nursing pig is adapted to this diet and produces lactase in high amounts. Between the age of 2 and 8 weeks, the amount of lactase gradually decreases and disappears as the nursing pig stops suckling. Concomitantly amylase and maltase needed to digest more complex carbohydrates like starch from corn or other cereals increase (43).

Digestive enzyme activity in the young pig

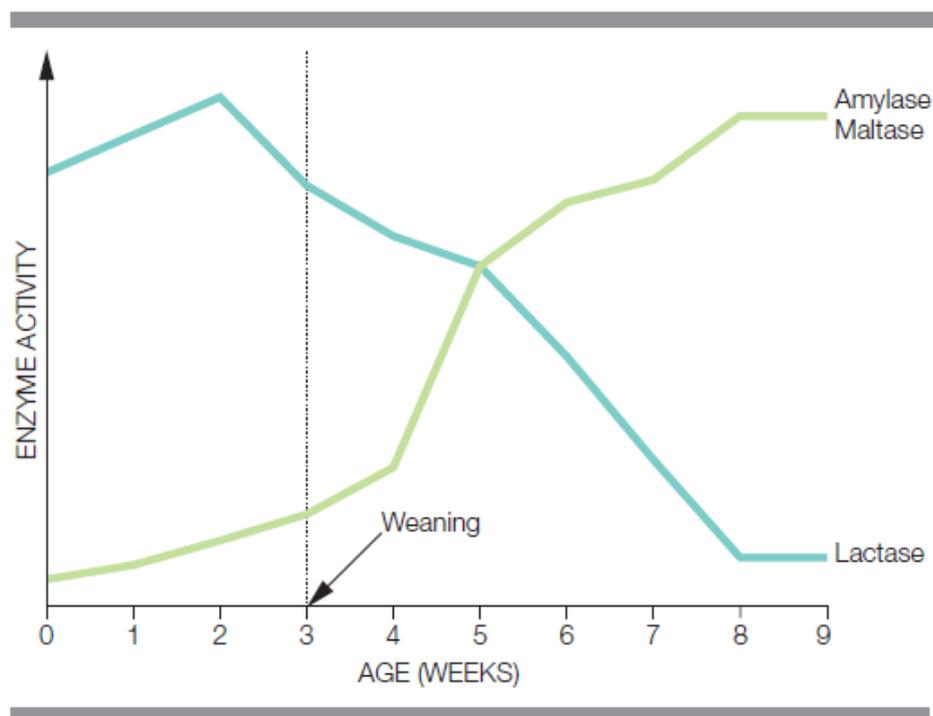


Figure 3. Digestive enzyme activity in the young pig (44).

During weaning, piglets are introduced to complex feed at 2 – 5 weeks of age depending on country and local practices. The digestive system has not matured to its final stage at this age and diarrhea is

often seen (45). Morphological studies of the digestive tract of the piglets show villus atrophy and crypt hyperplasia leading to decreased digestive and absorptive capacity.

Whey has been used to feed weanling piglets for decades. It has been speculated and discussed whether the beneficial effect of whey is mainly due to the lactose fraction or the protein fraction. Tokach (46) made a study that indicated that both fractions are important in explaining the beneficial response to dried whey.

Feeding studies (47 – 51) have shown that adding permeate to the diet of weanling piglets results in an increase in average daily feed intake (ADFI) and average daily weight gain (Average Daily Gain, ADG). The effect seems to be higher with younger piglets – where the amount of lactase is high and the amount of maltase and amylase is low (50). Some studies also find increased feed conversion rates (feed intake/weight gain) (48, 49) but other studies did not find changes in the feed conversion rate (47, 51). Improved nitrogen digestibility has been reported in some studies (48, 49). A study investigated the effect of replacing the lactose of spray-dried whey with pure lactose or deproteinized whey (= whey permeate) (52). Lactose (18%) was supplied as: a) 25% dried whey, b) 12.5% dried whey + 9% pure lactose, c) 18% pure lactose, d) 12.5 % dried whey and 10.9 % deproteinized whey or e) 21% deproteinized whey. The protein of the spray-dried whey was replaced with casein based on the amount of lysine in spray-dried whey and casein. The ADG was very similar in all groups, indicating that the source of lactose is of minor importance. Overall the digestive system of young pigs seems to favor digestion of lactose. The upper limit of the positive effect of lactose on weight gain depends on the composition and complexity of the food matrix.

The question is to what extent these studies and their results reflect the situation of the malnourished child. Malnourished children frequently have enteropathy with increased gut permeability, villus atrophy, crypt hyperplasia and moderate malabsorption (53) which seems to be similar to weanling piglets.

In contrast to suckling piglets, human infants have specific activities of maltase and sucrase which are two-fold and sixfold higher than that of lactase (54-57) and the intestinal maltase and sucrase activities develop already in utero (58). The “digestive advantage” of lactose compared to other carbohydrates is therefore less obvious.

Furthermore, in the above mentioned studies piglets received a feed that fulfilled their needs for essential amino acids, vitamins and minerals, protein etc. which the malnourished children do not. The role of substituting part of the feed (eg. corn/cereal) with lactose can therefore not be translated directly to the situation of the malnourished child.

The growth enhancing effect of lactose in weanling piglets has been repeated in several studies and lactose is used in the feed of piglets in many formulations. Human studies are needed to evaluate if and to what extent lactose promotes the growth of well-nourished and malnourished infants.

Animal studies of prebiotic effects

A prebiotic is defined as “a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health” (59)

Prebiotic effects have also been observed in weanling piglets receiving high amounts of lactose: 215 g/kg feed and 330 g/kg feed, equal to 23 E% and 32 E% respectively. The growth of bifidobacteria (60) and lactobacilli (61) was stimulated and the total amount of volatile fatty acids (SCFAs) was increased (61). The stimulation of lactobacilli and bifidobacteria depended on dosage, protein concentration and the presence of other fermentable carbohydrates.

The prebiotic effect described in piglets seems to be close to the prebiotic effects seen in humans (see page 9) and the results of lactose on intestinal morphology and microbiota changes will be used in the overall evaluation of lactose.

Malnourished piglets

Department of Human Nutrition has conducted a study with permeate in a malnourished pig-model. A poster showing the major results has been distributed to Arla Foods Ingredients and an article is under preparation.

The purpose of the study was to investigate if permeate and SMP prevented an expected drop in serum phosphate during refeeding of severely malnourished piglets with CSB+. CSB+ is currently used in the treatment of moderately malnourished children and hypophosphatemia is considered a critical risk during refeeding of malnourished children. Overall, the results showed that inorganic serum phosphate dropped during the first week of refeeding with CSB+ and returned to pre-refeeding levels after 2 weeks. In CSB+ supplemented with permeate (8%) or SMP (8%), no drop

in inorganic serum phosphate levels were observed. The levels of inorganic serum phosphate levels increased in the groups receiving CSB+ with permeate or SMP after 3 weeks compared to controls.

Potential applications of Variolac

The value of permeate in relation to treatment of malnutrition is linked to the high content of lactose and to a smaller degree the content of type II minerals (calcium, bioavailable phosphorus, magnesium and potassium). The content of protein and potentially bioactive milk substances (eg. peptides, oligosaccharides) is considered to be very low with no or very limited nutritional value.

We have evaluated permeate as a possible ingredient in existing types of food supplements for moderately malnourished children.

Permeate could be added to products for food aid which do not contain any form of sugar or permeate could be added to substitute sucrose or part of the sucrose which is currently used to increase the energy density and palatability of food aid for moderately malnourished children.

Lactose vs. sucrose

Different characteristics of lactose and sucrose have been collected in table 3. Lactose has a number of benefits compared to sucrose: First of all it is a natural ingredient in breast milk, where the lactose content is considerably higher than in cow's milk, it has prebiotic effects in lactase deficient individuals and may enhance mineral absorption of infants. Furthermore, it has a lower glycemic index and it is less cariogenic compared to sucrose. In addition permeate contains some growth minerals. The average market price of permeate is higher than sucrose and the price of pure lactose is even higher – also when taking the different concentrations of lactose of the two products into account.

	Sucrose	Lactose in permeate
General	-	Natural ingredient in breast milk
Energy density	3.9 kcal/g	3.9 kcal/g
Flavour	Very sweet	Dairy flavor
Sweetness	Index 100	Index 20 - 60*
Glycemic index	65	46
Dental effect	Very negative	Less negative
Prebiotic effect	No	Yes**
Enhances mineral absorption	No	Maybe
Intolerance in children below 5 years	Very rarely [#]	Rarely ^{##}
Price [□]	0.35 – 0.76 USD/kg (100 % sucrose)	0.6 – 1.0 USD/kg (85% lactose)

Table 3. Comparison of sucrose and lactose as ingredient in food supplement for moderately malnourished children

* Variolac/permeate is perceived sweeter than pure lactose due to an enhancing effect of sodium/minerals and has a dairy flavour

** Prebiotic effect seen in newborns and in populations with reduced lactase activity or lactase deficiency (transient or permanent)

Transient sucrose deficiency has rarely been observed in malnourished children.

Temporary lactose intolerance may be seen in malnourished populations with diarrhea. Caution in relation to lactose consumption may be needed in vulnerable malnourished children (eg. severely malnourished children with HIV and diarrhea)

□ Min/max price 2009 – 2011 based on USDA info/www.ers.usda.gov and data from Arla Foods Ingredients.

Permeate and fortified blended foods

Fortified blended foods (FBF) are widely used for treatment of moderate malnutrition and food insecure populations. FBF is distributed by World Food Programme (WFP). Corn soya blend (CSB) is the most commonly distributed blend followed by wheat soya blend (WSB). (See figure 4)

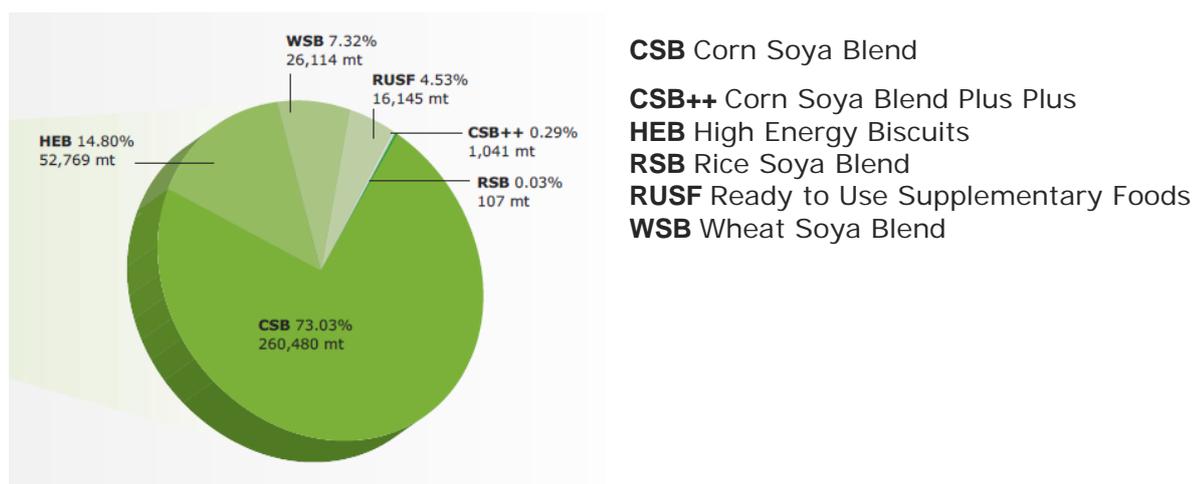


Figure 4. WFP procurement of blended foods in 2010 (62).

CSB and WSB were developed in the 1960's by the US Agency for International Development. The cereal and soya is precooked (preferably by extrusion) to reduce the amount of anti-nutrients, to facilitate easy preparation before ingestion and to reduce the need for firewood in the families. A mix of minerals and vitamins is added to FBF (4).

Concern about low micronutrient content, low energy density, high fiber and anti-nutrient content of these products and lower recovery rates compared to RUTF/RUSF led World Food Programme to initiate development of an improved version of CSB, CSB++, which is targeted for treatment of vulnerable children with moderate acute malnutrition at 6 – 24 months of age. The first clinical results have come out (7) showing very high and non inferior recovery rates of CSB++ (85.9%) compared to locally or internationally produced RUSF (87.7 and 87.9%, respectively) in a study in 2712 Malawian children.

However, the price of CSB++ is very high compared to the price of CSB. According to the Unicef procurement catalogue (63), the current cost of CSB++ is 2.53 USD/kg compared to 0.7 USD/kg of CSB+ (intended for older children and adults with MAM) and even lower prices for CSB (Example: 450 – 600 USD/ton (64).

Adding 20% of permeate to CSB without any other adjustments would increase the energy density of thin porridge prepared according to the World Food Programme recommendations by 20% (from 0.52 kcal/g to 0.625 kcal/g – for calculations see appendix I) and decrease the protein content from min. 37 g/1000 kcal to min 30 g/1000 kcal. The amount of calcium, phosphorus and potassium would increase to fulfill the recommended levels for food aid intended for moderately malnourished children between 7 – 59 months, whereas the amount of zinc and magnesium would need further supplementation to meet the recommended nutrient intake. If the price of permeate is 0.9 USD/kg when procured for manufacturing of food aid, the price of CSB with 20% permeate would increase from 0.50 – 0.70 USD/kg to 0.58 – 0.74 USD/kg if no extra processing steps are needed. The economic value of the minerals of permeate is very low.

Nutrient	CSB	CSB ++	CSB with 20% perm	Recommended Nutrient Intake, by Golden, (43)	Recommended Nutrient Intake, by WHO**
Price#	0.5 – 0.7 USD/kg	2.53 USD/kg	0.58 – 0.74 USD/kg	-	-
Energy	1000 kcal (263 g CSB)	1000 kcal (244 g)	1000 kcal (267 g CSB)	1000 kcal	1000 kcal

		CSB++)			
Fat	16 g (min)	22 g (min)	12.8 g (min)		25 – 65 g
Protein	37 g (min)	39 g (min)	30 g (min)	24 g	20 – 43 g
Fibre	Max 5%	Max 3%	Not available	Not available	Not available
Sodium	Not available	Not available	325 mg*	550 mg (max)	500 mg (max)
Potassium	1053 mg*	976 mg*	1812 mg*	1400 mg	1500 - 2200 mg
Magnesium	-	-	68 mg*	200 mg	280 - 420 mg
Zinc	13 mg	12 mg	11 mg	13 mg	20 - 35 mg
Phosphorus	526 mg*	488 mg*	780 mg*	600 mg	850 - 1400 mg
Calcium	342 mg*	317 mg*	587 mg*	600 mg	1000 - 1400 mg

Table 4. Nutrients/1000 kcal.

*Variable levels of micronutrients naturally present in maize and soya may lead to variable amount of micronutrients in finished product. The numbers are the added minerals.

** The WHO recommendations have not been published yet.

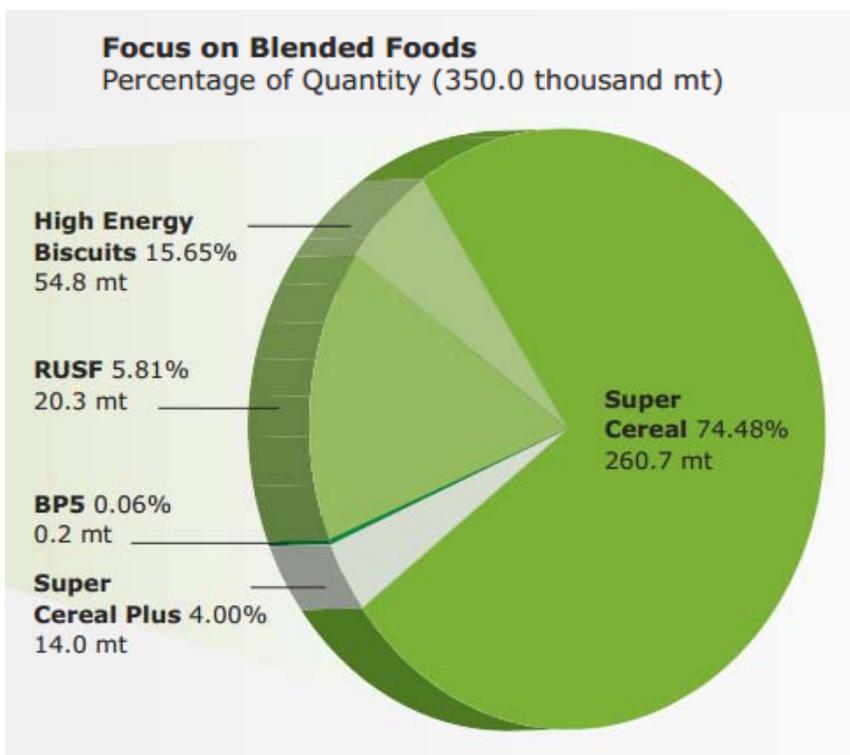
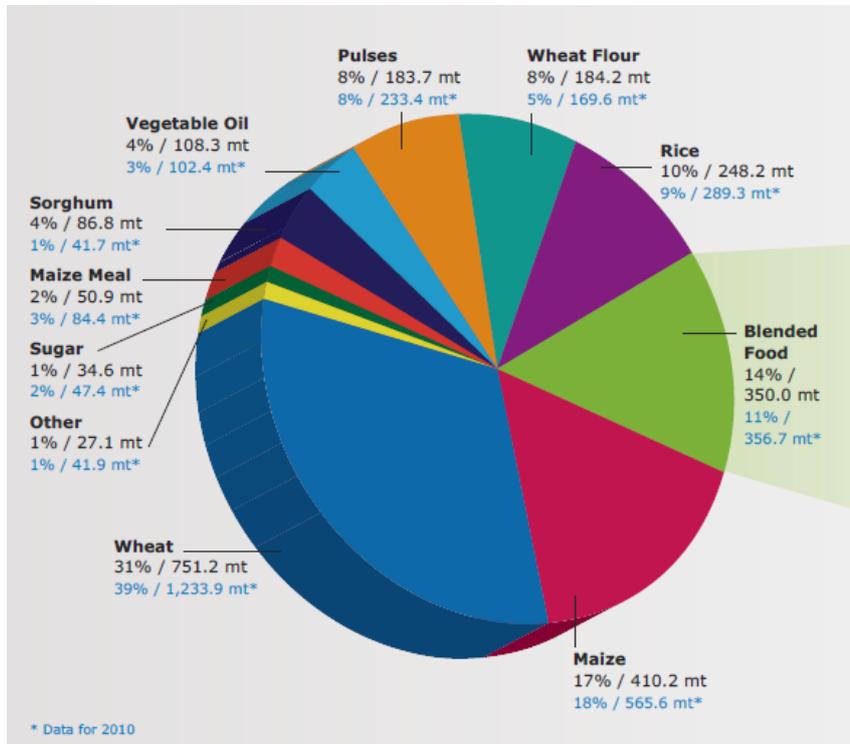
Other applications of permeate

Permeate could be added to the following products used in the treatment of moderately malnourished children:

- Ready-to-use-supplementary-food (RUSF) and ready-to-use-therapeutic-food (RUTF)
These products contain approx. 28 % of sugar and 30% of SMP/WP. The sugar could be fully substituted by permeate or substituted partly by permeate and partly by a digestible starch source.
- High energy biscuits
If permeate is not already used in manufacturing of biscuits, permeate could add a dairy flavor to the biscuits. High energy biscuits and compressed food bars are baked, energy dense biscuits/bars mainly used for emergency programs where access to cooking facilities is limited – eg. in the beginning of after a natural disaster.

Market evaluation

World Food Programme is the main distributor of FBFs (80% of the market or more). The 2011 procurement figures from WFP can be seen from figure 4 and 5 below.



Super Cereal includes: Corn Soya Blend, Rice Soya Blend and Wheat Soya Blend

Super Cereal Plus includes: Corn Soya Blend++ and Wheat Soya Blend++

Acronyms

BP5	Emergency Rations
CSB	Corn Soya Blend
CSB++	Corn Soya Blend Plus Plus
HEB	High Energy Biscuits
RSB	Rice Soya Blend
RUSF	Ready to Use Supplementary Foods
WSB	Wheat Soya Blend
WSB++	Wheat Soya Blend Plus Plus

Figure 5 and 6. World Food Programme procurement of food and blended foods in 2011 (65).

The total amount of FBF procured by WFP in 2011 was 350.000 ton, equal to 317.5 million US\$. The quantity of food purchased in 2011 was similar to the quantity of 2010 (see figure 3 for comparison), however in 2011 there was more focus on specialized products like CSB++. The amount of CSB++ increased from 1000 ton in 2010 to 14.000 ton in 2011 and the amount of RUSF increased from 16.145 ton in 2010 to 20.300 ton in 2011.

Below Appendix II shows the estimated global procured amounts of blended foods (FBF, RUSF and HEB) in 2011. The amount of milk powder included in these products and the value of both the milk powders and the blended foods are estimated.

Conclusion

Whey permeate contains mainly lactose and minerals (calcium, phosphorus, magnesium, potassium). The content of protein and potentially bioactive milk substances (eg. peptides, oligosaccharides) is considered to be very low with no or very limited nutritional value.

Potential benefits of whey permeate

Lactose

- Lactose is present in high amounts in breast milk and is the major carbohydrate source in feeding all mammals after birth
- Lactose can increase energy density of food for malnourished children
- Lactose has a lower cariogenicity compared to sucrose
- Lactose and permeate may increase food palatability
- Lactose has a beneficial prebiotic effect in individuals with reduced lactase activity. This includes adults with primary lactase deficiency, preterm infants with immature lactase activity, possibly term infants and may include malnourished children
- Lactose may increase mineral absorption in infants
- Lactose provided by permeate is cheaper than pure lactose but more expensive than sucrose
- Lactose has a growth promoting effect in piglets. Human studies are needed to evaluate if and to what extent lactose promotes the growth of well-nourished and malnourished infants

Minerals

- Permeate contains bioavailable calcium, phosphorus, magnesium and potassium, which are minerals important for growth.
- The nutrient:nutrient ratios are not identical to the recommended levels for malnourished children. Thus, the mineral mixes added to these products have to be adjusted.
- The savings of adding less minerals to these products is likely to be small.

Whey permeate potential drawbacks

- Lactose intolerance is a potential problem in malnourished children with diarrhea. However, for the majority of malnourished children between 6 months and 5 years of age, lactose intolerance is not regarded as a significant challenge if milk and lactose is provided in small frequent meals. In vulnerable patients like severely malnourished inpatients with HIV and diarrhea or enteropathy, further investigations are needed to evaluate if and to what extent lactose should be restricted or omitted temporarily due to the risk of osmotic diarrhea
- The price of permeate is slightly higher than the price of sucrose based on energy equivalent units.

Permeate could be added as an ingredient to existing types of food supplements for moderately malnourished children. This includes among others fortified blended foods, ready-to-use-food and high energy biscuits. The amount should be balanced not to dilute nutrient content of other ingredients too much and not to reach upper limits for the intake of lactose and minerals, especially sodium.

Overall permeate could be used in food aid for moderately malnourished children mainly as a “natural carbohydrate source”. This would increase the energy density and possibly the palatability of the food, have a reduced cariogenic activity compared to sucrose and potentially have a prebiotic effect.

Studies are needed to identify relevant doses in malnourished infants where the taste, potential prebiotic activity and risk of osmotic diarrhea and growth are evaluated.

Further studies could be made to investigate the cariogenic activity of food aid with lactose compared to sucrose in malnourished children.

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Appendix I Calculations – energy density

Energy density increases with addition of lactose or other carbohydrates that does not take up water.

Recipes of thin porridge

Recipes according to World Food Programme:

40 g CSB and 250 g water for CSB thin porridge

50 g CSB++ and 250 g water for CSB++ thin porridge

Calculated recipe for CSB + 20% permeate

$0.80 (40 \text{ g CSB} + 250 \text{ g water}) + 0.20 (40 \text{ g permeate}) =$

$32 \text{ g CSB} + 8 \text{ g permeate} + 240 \text{ g water}$

Energy density of CSB powder: 380 kcal/100 g powder

Energy density of CSB thin porridge:

- **40 g CSB/290 g thin porridge x 380 kcal/100 g CSB = 0.52 kcal/g thin porridge**

Energy density of CSB++ powder: 410 kcal/100 g powder

Energy density of CSB++ thin porridge:

- **50 g CSB++/300 g thin porridge x 410 kcal/100 g CSB++ = 0.68 kcal/g thin porridge**
- **Improvement compared to CSB thin porridge: $(0.68-0.52)/0.52 \times 100\% \approx 30\%$**

CSB + 20% permeate: $(0.80 \times 380 \text{ kcal/100 g} + 0.20 \times 353^* \text{ kcal/100g}) = 375 \text{ kcal/100g}$

Energy density of CSB + 20% permeate thin porridge

- **40 g CSB + permeate/240 g thin porridge x 375 kcal/100 g = 0.625 kcal/g**
- **Improvement compared to CSB thin porridge: $(0.625-0.52)/0.52 \times 100\% \approx 20\%$**

The energy density of permeate is 1480 kJ/100 g equivalent to 353 kcal/100g

Appendix II Estimated milk powder market and total market for blended foods

	Total Quantities	Content of milk	Value of milk powder	Price/kg of final product	Value of final product UN organisations
FBF (WFP) <ul style="list-style-type: none"> • CSB/WSB • CSB+ • CSB++ 	260.100 MT - 14.000 MT (1000 MT in 2010)	0% (20% Perm) 0% 8% SMP	0 (36-47 mio\$ ¹) 0 3.1 mio \$	0.5-0.6 \$/kg 0.7 \$/kg 2.53 \$/kg	130-180 mio \$ 35 mio \$
RUSF/RUTF (Unicef + WFP)	20.000 MT (WFP: RUSF) 10.000 MT (unicef RUSF estimate) ² 27.000 MT (unicef: rutf)	30% SMP/WP 30% SMP/WP	35.5 mio \$ ³	RUSF: 3.2 \$/kg RUTF: 3.91 \$/kg	64 mio \$ (WFP 2011) ⁴ 137 mio \$ (Unicef 2011) ⁵
HEB (WFP)	54.000 MT (WFP)	Not available	Not available	13.15 \$/20 x 400g = 1.65 \$/kg	90 mio \$ ⁶
Total market					500 mio \$/0,8 = 625 mio \$

Comments:

The quantities and market values are based on WFP and Unicef procurement reports. Numbers are from 2011 unless stated otherwise. WFP and Unicef constitutes approximately 80% of the world market for food aid.

Plumpy Doz 43\$/36 x 325 g = 3.67 \$/kg,

Plumpy Sup 42.1\$/150 x 92 g = 3.04 \$/kg.

RUSF: Plumpy'Doz + Plumpy'Sup. Estimated price/kg RUSF: 3.20 \$/kg as more Plumpy'Sup is used compared to Plumpy'Doz.

Plumpy Nut 54 \$/150 x 92 g = 3.91 \$/kg

1) If 20% whey permeate is added to all CSB/WSB: 260.100 MT x 10³ kg/MT x 0.2 x (0.7 - 0.9) \$/kg = 36 – 47 mio \$

2) Value 24 mio USD x 4/3 quarters = 32 mio USD converted to MT: 32 mio USD/3.2 \$/kg = 10.000 MT

3) Assuming 15% SMP + 15% SWP + April 2012 prices: 57.000 MT x 10³ kg/MT x (0.15 x 2.80 \$/kg + 0.15 x 1.35\$/kg) = 35.5 mio \$

4) RUSF WFP: 20.000 MT x 10³ kg/MT x estimated 3.2 \$/kg = 64 mio \$

5) 27.000 MT x 10³ kg/MT x 3.91 \$/kg + 24.000 \$ x 4 quarters/3 quarters = 137 mio \$

6) HEB: 54.800 MT x 10³ kg/MT x 13.15\$/8kg = 90 mio

