Infant Nutrition

Presentation to the Society of Dairy Technology at the 70th Anniversary Conference Whey Technology & Utilization

Wednesday 12th June 2013

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Wyeth Nutrition

Overview

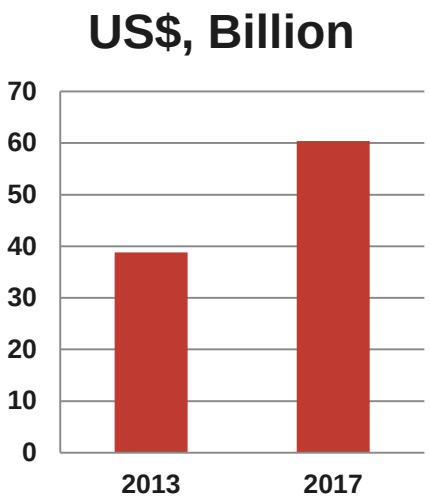
1. Background

2. Whey-derived Ingredients used in Infant Formula

Safety & Trust

Market Landscape

Baby food market projected to grow



Global sales of baby food are currently estimated at $38.8 BN and expected to expand to $60.4 BN by 2017 (Euromonitor)

Key growth drivers

- World Population Growth
- Demographic shifts
- Emerging markets for growth

Details

2013: 7.1 Billion

2050: 10.5 Billion

- Increased number of working mothers
- Rural to urban
- Lower to middle class affluence

- South East Asia
- India
- Africa, Middle East
- Latin America

Key Players

Manufactures of Infant formula

Major Multi-Nationals

Abbott Nutrition · Danone Baby Nutrition · Mead Johnson Nutritionals · Nestlé Nutrition · Wyeth Nutrition

Other Multi-Nationals (not exhaustive)

Arla · HiPP organic · Novalac · Fonterra · Heinz For Baby · aspen Nutritionals · Perrigo Nutritionals · FrieslandCampina · Hero Baby · Holle · ORDESA Group · meiji · Murray Goulburn · Humana · morinaga · Tatura · Snow Brand · HiPP organic

Local Producers (e.g. China) (not exhaustive)

Beingmate 中文 English · 光明乳业 Bright Dairy · Yashili 雅士利 · Mengniu 蒙牛 · Synutra 圣元 · Biostime 合生元 · 伊利

Nutritional Products

A broad range of products are available for multiple nutritional requirements

Maternal Nutrition

- During pregnancy or lactation
- Complimentary or, supplementary nutrition

Infant Formula (0-6 months)

- Sole source of nutrition
- Whey protein or, casein dominant
- Hydrolysed protein

Follow-on Formula (6-18 months)

- Weaning

Growing Up Milks (1 year +)

- Complimentary or, supplementary nutrition
- Flavoured milks

Pre-term Nutrition

- Low birth weight
- Human milk fortifier
- Post discharge formula

Special Medical Needs

- Elemental diets
- Metabolic conditions (e.g. PKU)
- Extensively hydrolysed protein

Mild to Moderate Feeding Intolerances

- Lactose-free
- Reduced lactose
- Soy protein
- Partially hydrolyzed protein
- Anti-regurgitation
- *Picky eaters*

Regulatory Environment

Composition

- Example: CODEX (2007) – CODEX Alimentarius
  - Commission created in 1963 by FAO and WHO to develop food standards, guidelines
  - Global recommendations
  - General but not universal adoption into legislation/regulation (adoption varies by country)
- Others: EU IF Directive, China GB Standards, US FDA, FSANZ...
- Varies by product, age, classification, country
- Infant (4-6 months); Follow-on Formula (FOF – after 6 months)

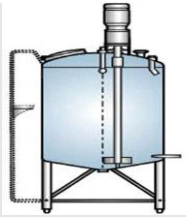
Labeling

- Varies by country and classification
- Evolving requirements for "Health Claims"
- Health Claims most defined in US (FDA) and EU (EFSA)

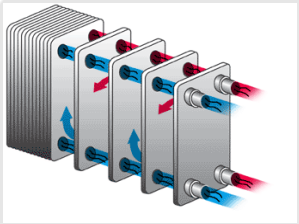
Marketing

- WHO Code - International Code of Marketing of Breast-milk Substitutes
  - General adoption into legislation/regulation, but not universal, some more strict
  - Varies by country and by age, classification
- FTSE 4 Good
  - globally recognised corporate responsibility standards

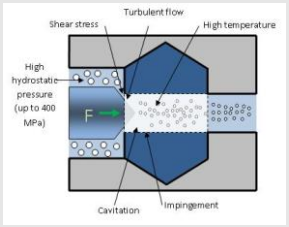
Manufacturing & Packaging – Core Technologies



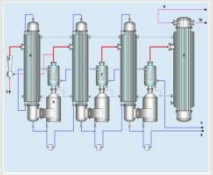
Recombining



Heat Treatment

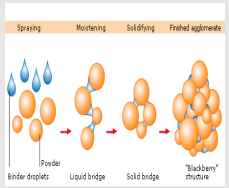


Homogenization



Evaporation

Spray Drying

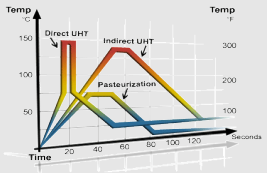


Agglomeration

Dry Blending

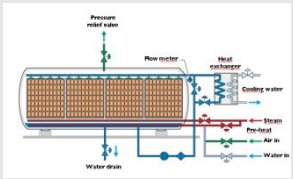
Dry Addition

Packaging



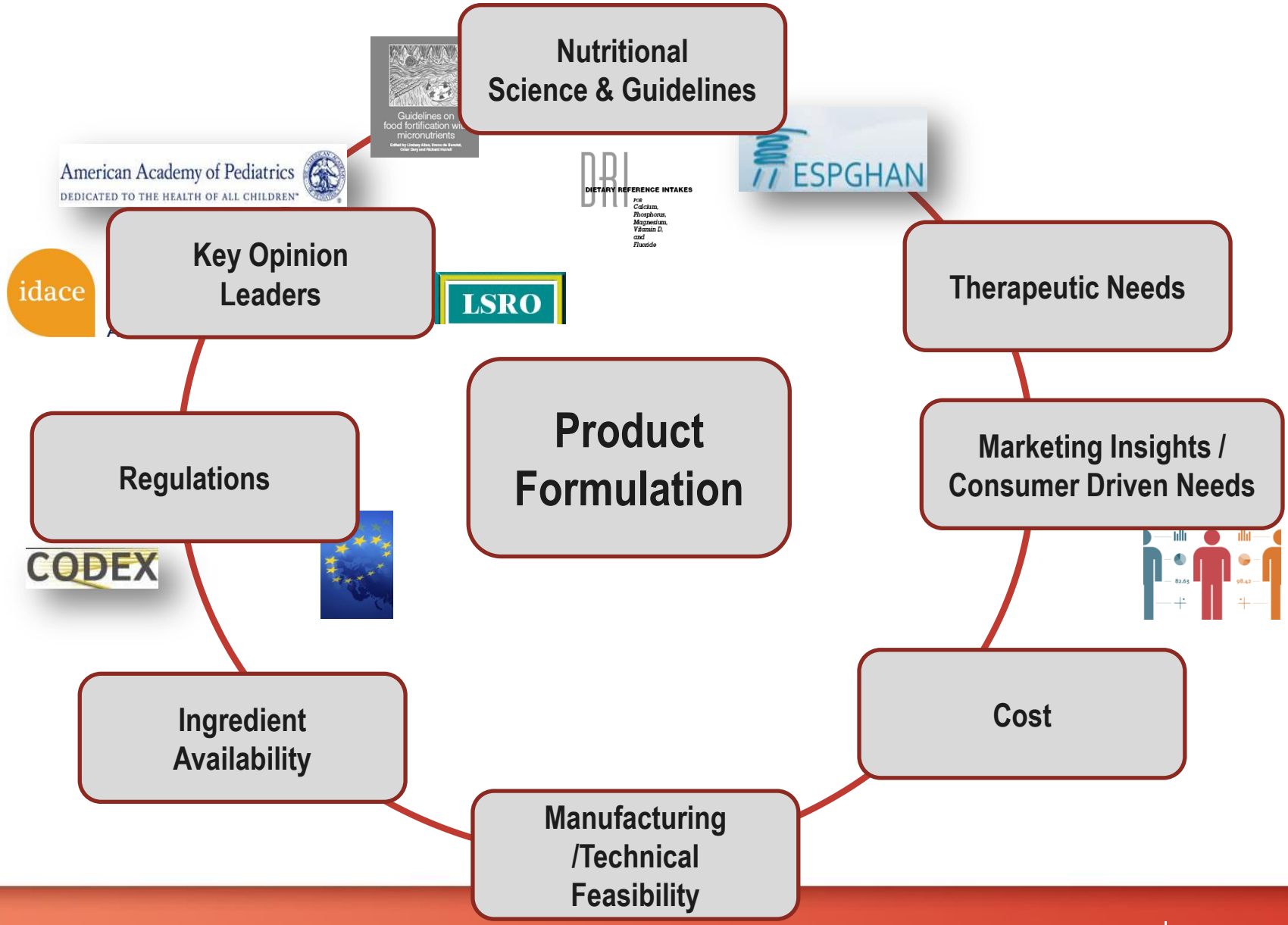
UHT

Aseptic Packaging



In-container sterilization

Formulation Considerations



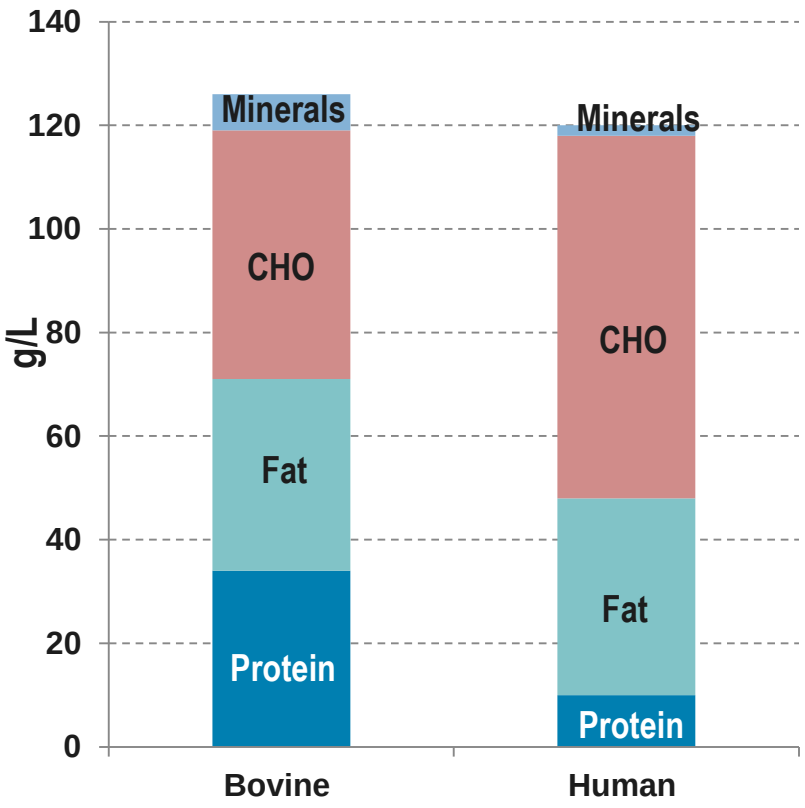
Overview

1 Background

2 **Whey-derived Ingredients used in Infant Formula**

Human Milk v Bovine Milk

Macro-composition of bovine and human milk



Component	Unit	Bovine	Human
Carbohydrate	g/L	48	70
Lactose	g/L	48	60
Oligosaccharides	**g/L**	Trace	**8-15**

Component	Unit	Bovine	Human
Whey : casein	--	**20/80**	**60/40**
NPN, as % TN	%	**5-6**	**20-25**
β-lactoglobulin	**g/L**	**3.2[1]**	**Absent**
α-lactalbumin	**g/L**	**[1]1.2**	**2-3[3]**
Serum albumin	g/L	0.4[1]	0.9[4]
Lactoferrin	**g/L**	**0.1[1]**	**2-4[3]**
Lysozyme	g/L	Trace [2]	0.04-0.09[3]
Lactoperoxidase	%	0.03[2]	Trace
Immunoglogulins	g/L	0.8[1]	1[2]

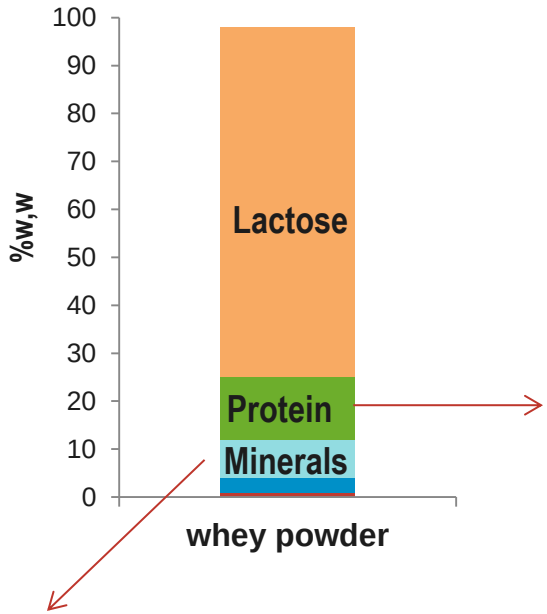
[1]Walstra *et al* (1999), [2]Renner *et al* (1989), [3]Harzer & Haschke (1989), [4]Sanchez-Pozo *et al* (1986)

Milk-derived ingredients used in infant formula

Ingredient	Application
Skimmed Milk	Casein source
Demineralized Whey	Whey protein source
Whey Protein Concentrate	Whey protein source
Alpha Lac - enriched WPC	α-lac enriched whey-dominant formulas
Lactose	Carbohydrate source
Partially Hydrolysed Whey Protein	Formulas for infants with mild-moderate feeding intolerances
Extensively Hydrolysed Whey Protein	Formulas for infants allergic to cow's milk protein
Milk Protein Isolate	Low Lactose formulas
Lactose free WPC	Lactose-free formulas
Galactooligosaccharides	Prebiotic containing formulas

Whey Powder

Composition of whey powder



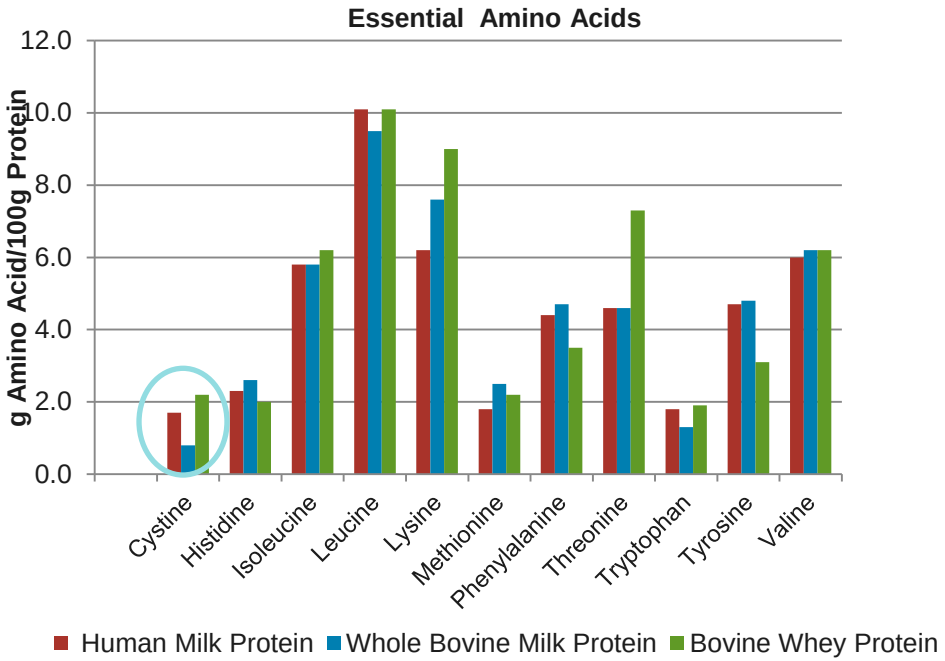
Whey powder contains a high mineral content

- **8-12% w/w**
- **Unsuitable for infant formula**

Demineralization required

Whey protein is a high quality protein

- **Biological Value** (BV)
- **Net Protein Utilization** (NPU)
- **Protein Efficiency Ratio** (PER)
- **Nitrogen Balance** (NB)
- **Protein digestibility** (PD)
- **Protein Digestibility Corrected Amino Acid Score** (PDCAAS)



Heine WE, Klein PD, Reeds PJ. The Importance of alpha-Lactalbumin in Infant Nutrition. J Nutr. 1991;121:277–283

Demineralized whey

Demineralization facilitated the development of a formula with a whey-to-casein ratio of 60:40

- Electrodemineralization
- Ion-exchange (IX)

Component (wt %)	Whey powder	Demin Whey powder (ED)	Demin Whey powder (IX)
Lactose	73	77	80
Protein	13	14.5	13
Lipid	1	1	1
Mineral	**8**	**4.5**	**1**
Moisture	3	3	3
Calcium	0.6	0.5	0.05
Magnesium	0.2	0.1	0.02
Phosphorus	0.6	0.5	0.15

Ref. De Wit (2001). Lecturers handbook on whey

Demineralization Timeline:

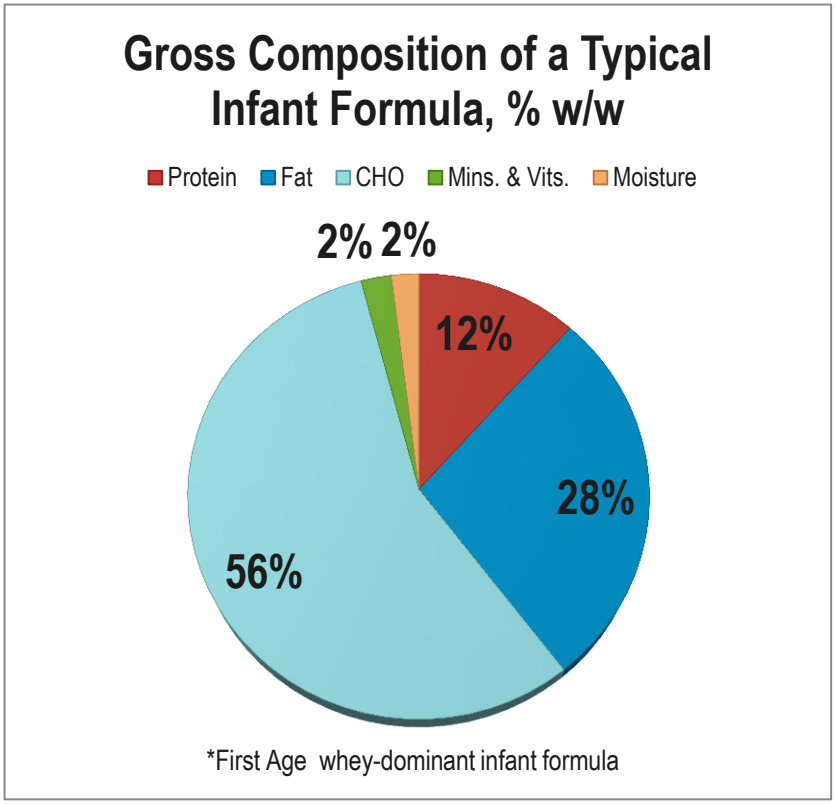
1948
Development of ion-exchange membranes

1950
Development of ED technology

1950
Wyeth & Foremost develop ED technology for whey demineralization with Ionics

1961
Wyeth develops the 1st commercially available infant formula with a whey-to-casein ratio of 60:40

Typical Infant formula composition



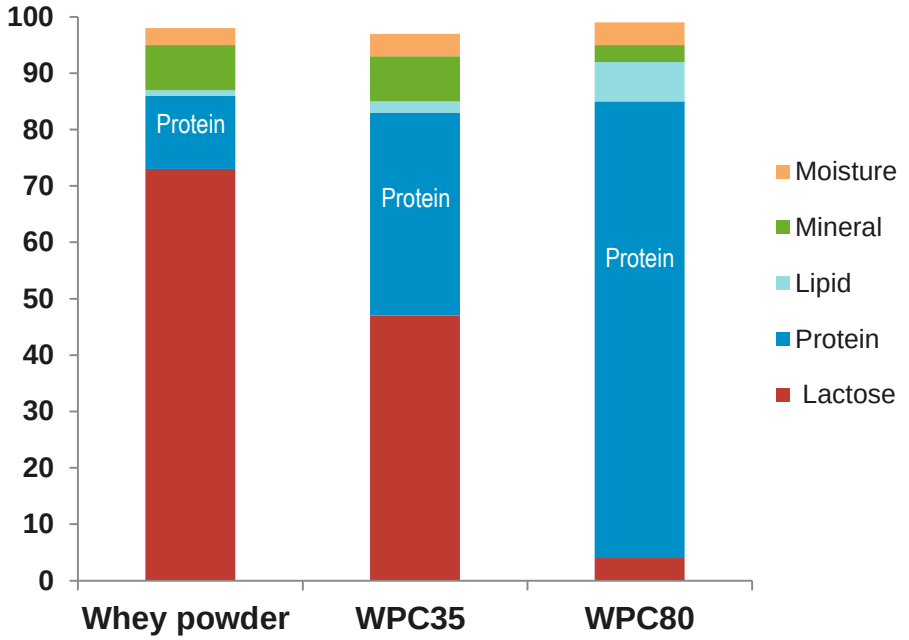
Demineralized whey and lactose account for >50% of the dry wt of the formula

INGREDIENTS*:

•Reduced minerals whey, vegetable oils, skimmed milk powder, **lactose,** soy lecithin, long-chain polyunsaturated fatty acid from single-cell source (arachidonic acid (AA), docosahexaenoic acid (DHA)), taurine, nucleotides (cytidine-5'-monophosphate, disodium uridine-5'-monophosphate, adenosine 5'-monophosphate, disodium inosine-5'-monophosphate, disodium guanosine-5'-monophosphate), l-carnitine, mixed tocopherols, concentrate, ascorbyl palmitate, lutein, minerals (sodium citrate, calcium chloride, magnesium chloride, calcium carbonate, potassium bicarbonate, potassium citrate, sodium phosphate, potassium hydroxide, potassium chloride, calcium hydroxide, ferrous sulfate, sodium chloride, zinc sulphate, copper sulfate, potassium iodide, manganese sulfate, sodium selenite), vitamins (ascorbic acid, choline chloride, inositol, alpha tocopherol acetate, niacinamide, pantothenic acid, vitamin A palmitate, thiamine hydrochloride, riboflavin, pyridoxine hydrochloride, cholecalciferol, natural carotenes, folic acid, vitamin K, biotin, cyanocobalamin)

Whey protein concentrate

Application of Ultrafiltration technology led to the development of WPC suitable for infant formula manufacture



Ref. De Wit (2001). Lecturers handbook on whey

Levels of Protein in WPC > Whey

↓

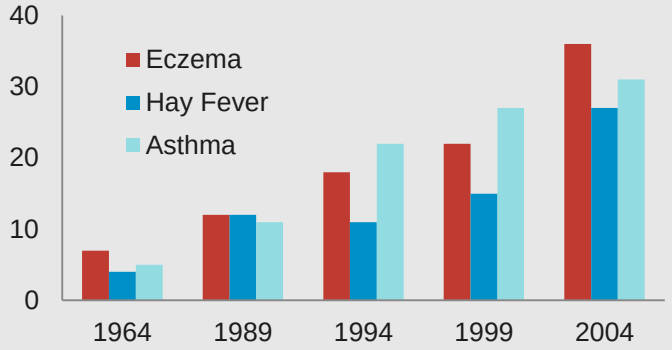
A reduced amount of ingredient required to achieve protein content

(less minerals incorporated into the formula with WPC than WP)

Hydrolysed whey protein

- **Allergies - a growing health issue**
  - Milk protein is a recognized allergen in the first year of life
  - Cows milk protein allergy is the most common such allergy
  - 3x increase in the prevalence of eczema in the last 15 years

Population: Aberdeen children 9-12 years
McNeil *et al*, 2009. Paediatr Perinat Epidemiol., 23(6):506-12



- Milk proteins may be enzymatically hydrolysed to reduce molecular weight, peptide size, and, consequently, their allergenicity
- Hydrolysed-protein formulas are generally categorized into **extensively** and **partially** hydrolyzed:

Partially hydrolyzed oligopeptides with a Mol. Wt. < 5,000 daltons*

Extensively hydrolyzed contain only peptides with a Mol. Wt. < 3,000 daltons*

Greer et al, 2008. Pediatrics Vol. 121, 183 -191.

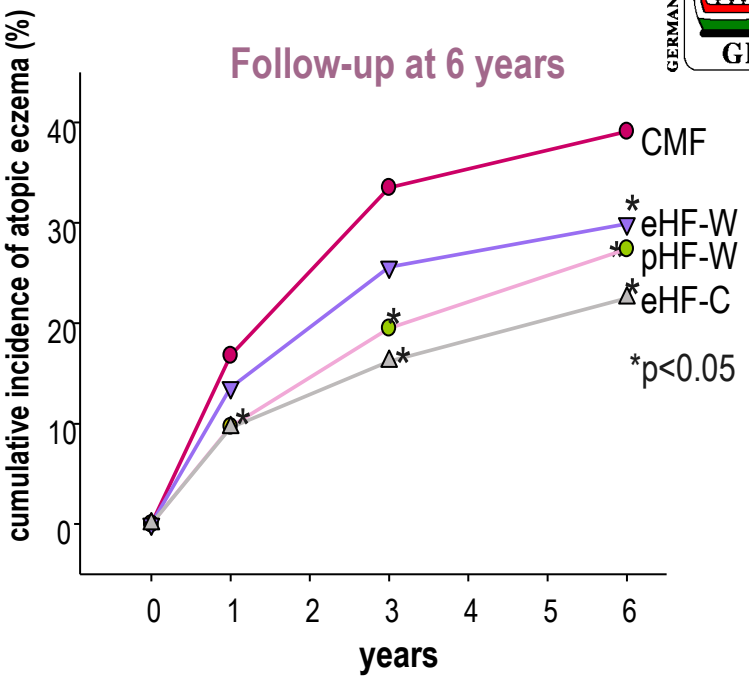
German Infant Nutritional Intervention (GINI) study

Subjects:

- In absence of breast milk
- 1995-1998 - newborns (n=2,252) with family history of allergy were randomly assigned one of 4 formulas
  - Partially Hydrolysed Whey Formula : pHF-W
  - Extensively Hydrolysed Casein Formula : eHF-C
  - Extensively Hydrolysed Whey Formula : eHF-W
  - Cows Milk Formula (CMF)

Outcomes:

- Physician diagnosed allergic diseases



Data confirm a long-term allergy-preventive effect of hydrolyzed infant formulas on allergic manifestation and atopic eczema until 6 years of age

Von Berg et al. J. Allergy Clin. Immunol. 2003, 2007, 2008

In absence of breast milk, numerous agencies recommend partially hydrolyzed formula for the prevention of atopic dermatitis

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

*"Atopic dermatitis may be delayed or prevented by the use of extensively or **partially hydrolyzed formulae,** compared with cow milk formula, in early childhood."*

ESPGHAN

*"…if exclusive breast feeding is not possible, it is recommended that a **hypoallergenic formula** should be used as a dietary allergy preventive measure in high risk infants…"*

EAACI
EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY

*"…in absence of breast milk, **formulae with documented reduced allergenicity** for at least the first 4 months, combined with avoidance of solid food and cow's milk for the first 4 months…"*

SOCIÉTÉ FRANÇAISE DE PÉDIATRIE

*"…prevention consists of feeding at-risk newborns until the age of 6 months with a **hypoallergenic formula**, provided that its efficiency has been demonstrated by well-designed clinical trials."*

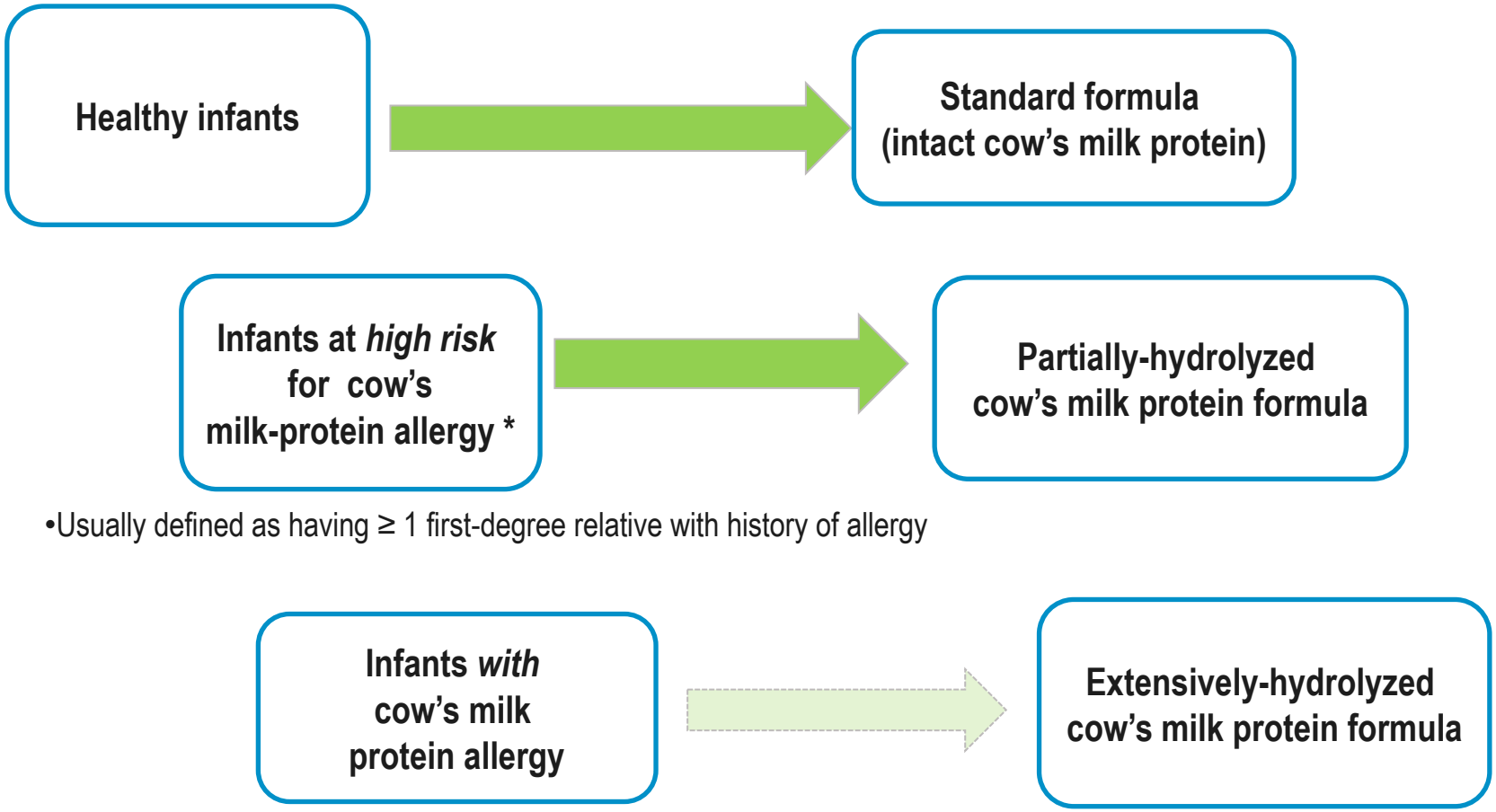
AWMF

*"...the feeding of **a partially or extensively hydrolysed formula is recommended** for infants at risk of allergy until 4 months of age..."*

SOCIÉTÉ FRANÇAISE DE PÉDIATRIE

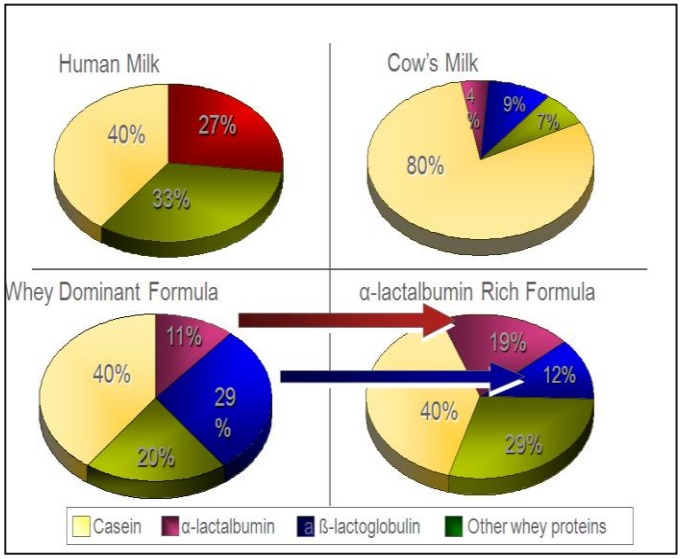
*"...for infants **where the allergic risk is not known at birth**, and where exclusive breast feeding is not possible, it is justified to give a **clinically proven hypoallergenic infant formula** until the family risk of allergy is known."*

In absence of breast milk – General Recommendations for preventing / treating allergy



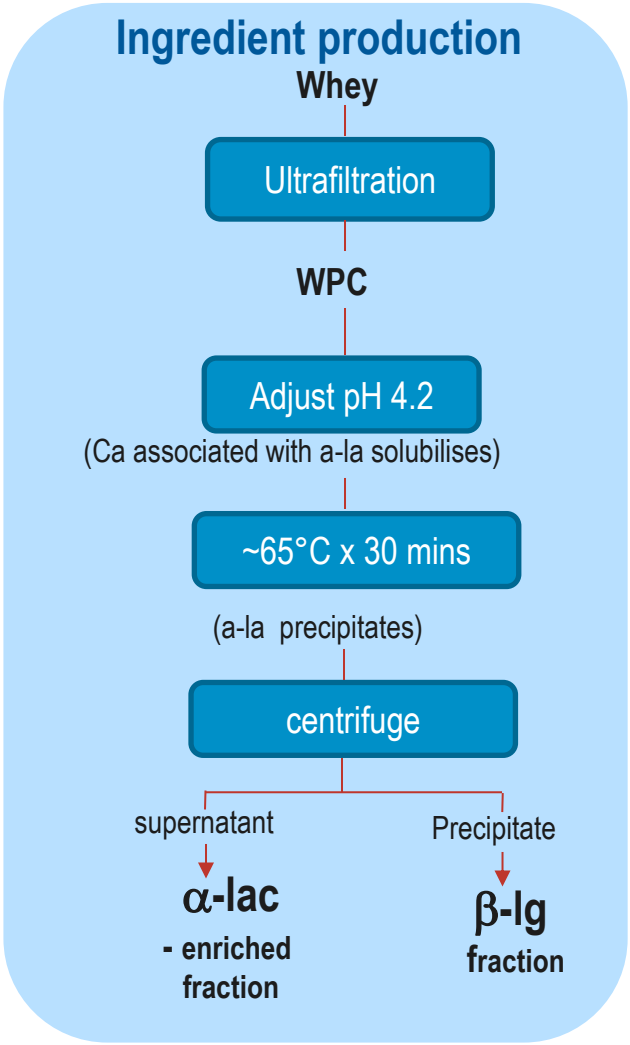
α-lactalbumin enriched whey protein

- **α-lactalbumin:** main whey protein in human milk



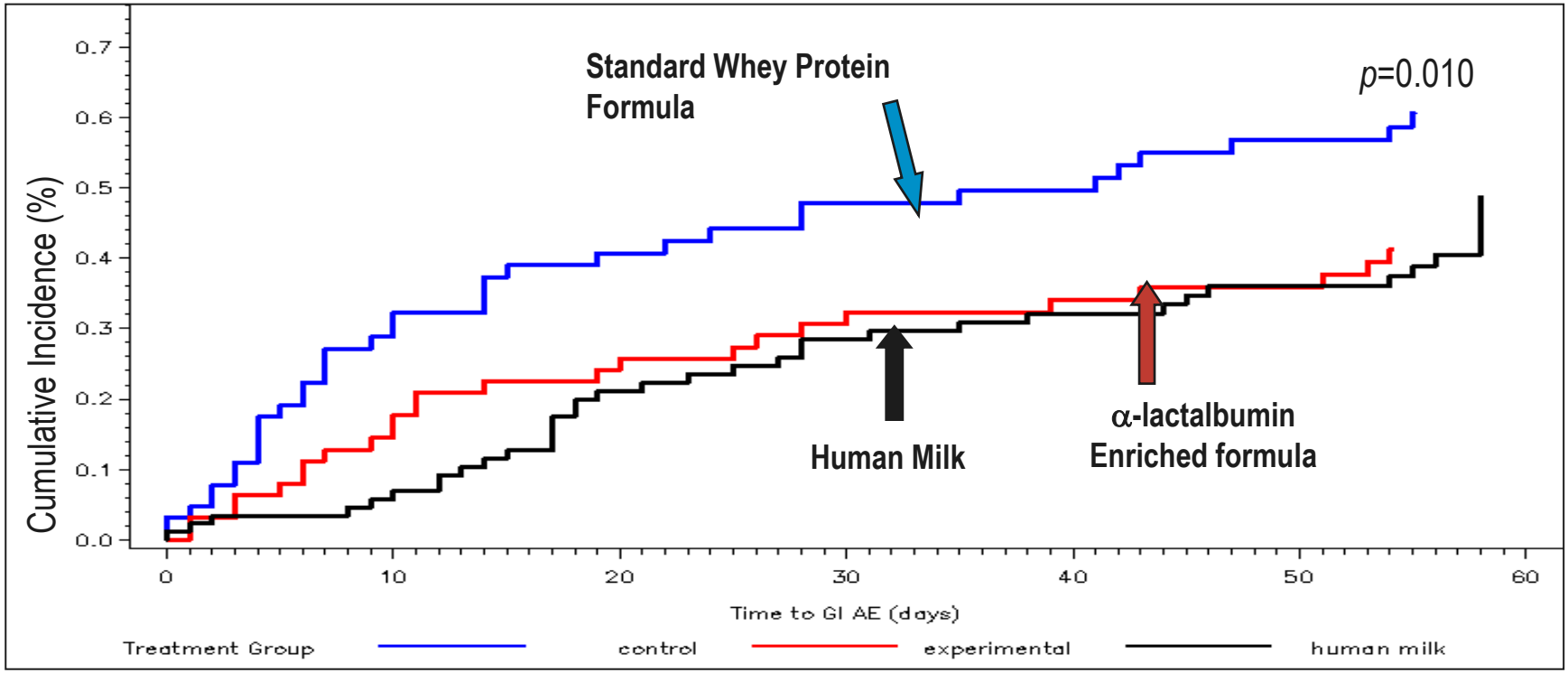
- Contains high levels of **tryptophan** and other essential amino acids, thus, facilitating the design of a lower protein formula (13-14 g l^{-1}) than when using demineralised whey

- **Enrichment/Isolation**
  - Chromatography
  - Selective aggregation of α-lac or β-lg followed by centrifugal or Membrane separation



[1]Ref: Pearce (1983). Aus. J. Dy Technol. 38: 144–149.

Cumulative Incidence of GI Study Events



Infants Fed α-Lactalbumin Enriched Formula Show GI Tolerance Similar to a HM Fed Infant

Davis AM et al. *Eur J Clin Nutr*. 2007.

Lactoferrin

Anti-Infection

LF reduces bacterial and viral pathogens from binding to epithelial layers

Gut Flora

LF enhances growth of some Bifidobacteria and reduces Clostridia and Candida

Immune Modulation

LF stimulates proteins (cytokines) that boost the immune system

Other

LF reduces oxidative stress in cells

Gut Function

LF stimulates intestinal epithelial cell proliferation

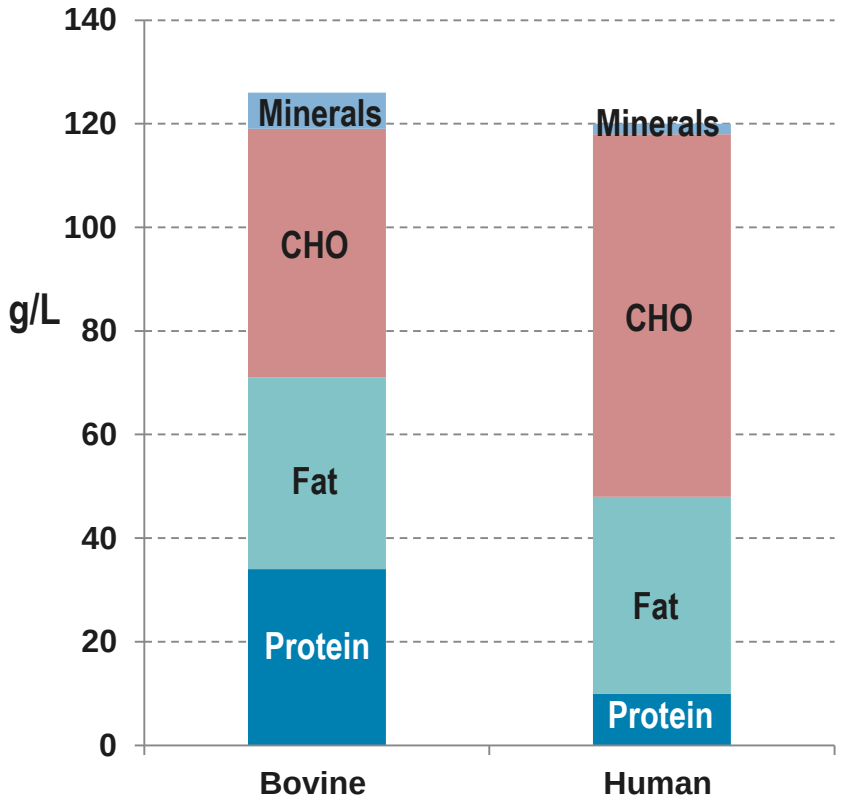
EFSA 2012: The Panel concludes that the novel food ingredient bLF is safe under the proposed uses and use levels.

Ref: EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA); Scientific Opinion on bovine lactoferrin. EFSA Journal 2012;10(7):2811.

Oligosaccharides

- **General**
  - Abundant in human milk (8-15 g/L)
  - >130 different oligosaccharides have been identified in human milk
  - Trace levels in bovine milk/whey
- **Functions**
  - Neural development (brain and spinal cord)
  - Prebiotics
  - Protect against enteric infection
- **Production/Isolation**
  - Galactooligosaccharides: enzymatically synthesized
  - Bovine Milk Oligosaccharides: 'mined' from dairy streams
  - Human Milk Oligosaccharides: chemically synthesized
  - Human Milk Oligosaccharides: microbial fermentation

Component	Unit	Bovine	Human
Carbohydrate	g/L	48	70
Lactose	g/L	48	60
Oligosaccharides	**g/L**	Trace	**8-15**



Oligosaccharides

- **Structure**
  - Complex carbohydrates (3 or more monosaccharides)
  - Contains 5 different types of sugars in their structure
    - **Glucose, galactose, glucosamine, fucose, and sialic acid**

- **Composition**

Major Oligosaccharides	Human Milk, g/L	Bovine Milk, g/L	
2'-Fucosyllactose	2.0*	-	Neutral
3'-Fucosyllactose	0.07	-	
Lacto-N-tetraose	1.09	Traces	
Lacto-N-fucopentaose I	1.26	-	
Difucosyllacto-N-hexaose II	0.16	-	
3'-Sialyllactose	0.17**	0.03-0.06***	Acidic/ Sialylated
6'- Sialyllactose	0.36**	Traces	
Sialyllacto-N-tetraose a	0.14	Traces	
Sialyllacto-N-tetraose c	0.17	Traces	
Total OS (incl. non-identified)	8 - 15	Traces	

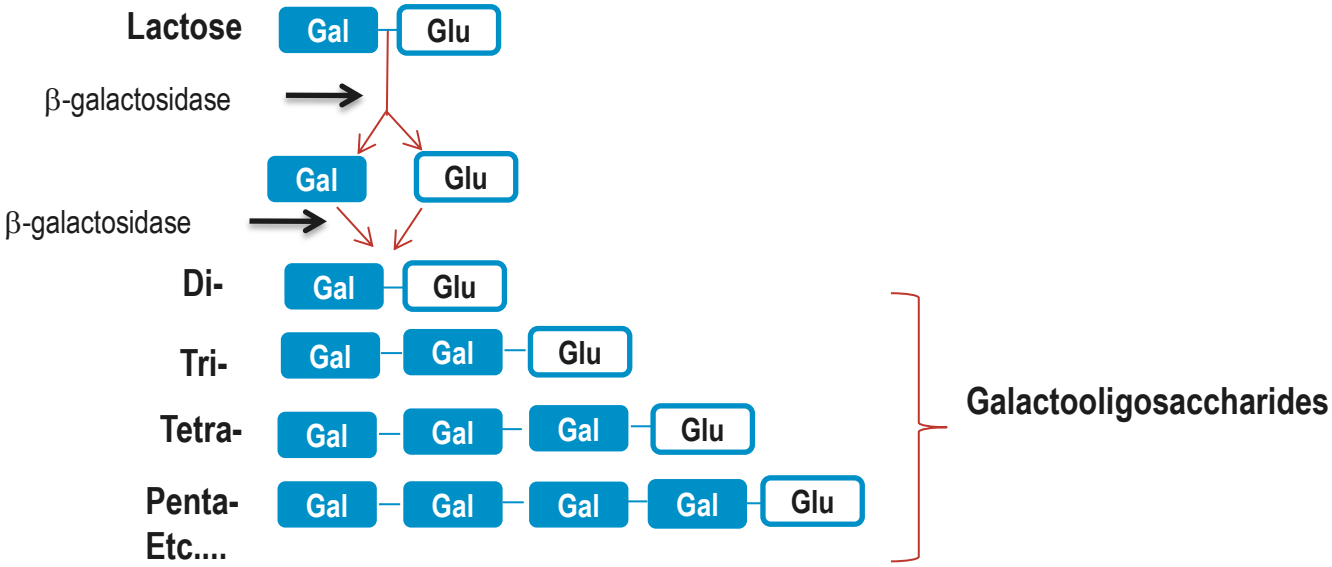
Sialyllactose is main OS found in bovine milk

Modified according to Kunz *et al* 2001

*Wyeth Nutrition Lit Survey Median Level, **Wyeth Nutrition Internal Data, ***Nakano et al- measured 3' + 6' SL

Galacto-Oligosaccharides (GOS)

- Manufactured from lactose via a transgalactosylation reaction catalyzed byβ-galactosidase
- Contains GOS plus lactose, dextrose (glucose) and galactose



- GRAS status
- Prebiotic
- Numerous clinical trials

Other Interesting Milk/Whey Components

Osteopontin

- Glycosylated protein
- **Human milk > bovine**
- Immune function
- Bone mineralization & growth

Lactophorin

- Glycosylated protein
- Not in human milk
- Immune function

Lactadherin

- MFGM protein
- **Higher levels in early milk**
- Human rotavirus inhibitor

Immunoglobulins

- Group of large glycoproteins
- Human milk: mainly sIgA
- Display antibody activity
- **Heat labile**

Glycomacropeptide

- Casein-derived whey glycophosphopeptide
- **Rich in sialic acid**
- Prebiotic
- Anti-infective
- Unique AA profile:
- Low-Phe diet
- Diet for hepatic diseases.

TGF-β

- Protein (cytokine)
- Growth factor
- Cell signalling
- Immune function
- Anti-inflammatory

Concluding Remarks

- Ingredients derived from whey, in particular whey protein with its **high protein quality**, have traditionally been important ingredients for the production of infant formula
- New Developments
  - There will be a continuous endeavour by scientists to understand the **biologically active components** in whey and the **potential benefit** of these components on the **growth and development** of infants and young children
  - Ingredient and formula producers must overcome the **challenges** to developing innovative and impactful nutritional solutions:
    - **Technological challenges**
      - Development of enrichment strategies for large scale supply
      - Preservation of functionality throughout isolation and processing
    - **Economical challenges**
      - Plentiful supply at cost-effective price
    - **Clinical challenges**
      - Demonstration of efficacy – meaningful claims
    - **Regulatory challenges**