An abstract graphic featuring several clusters of colorful spheres (pink, orange, blue, purple, yellow, green) connected by thin white lines, resembling a molecular or network structure, set against a teal background.

Allergy management and discomfort reduction

– with milk protein
hydrolysates

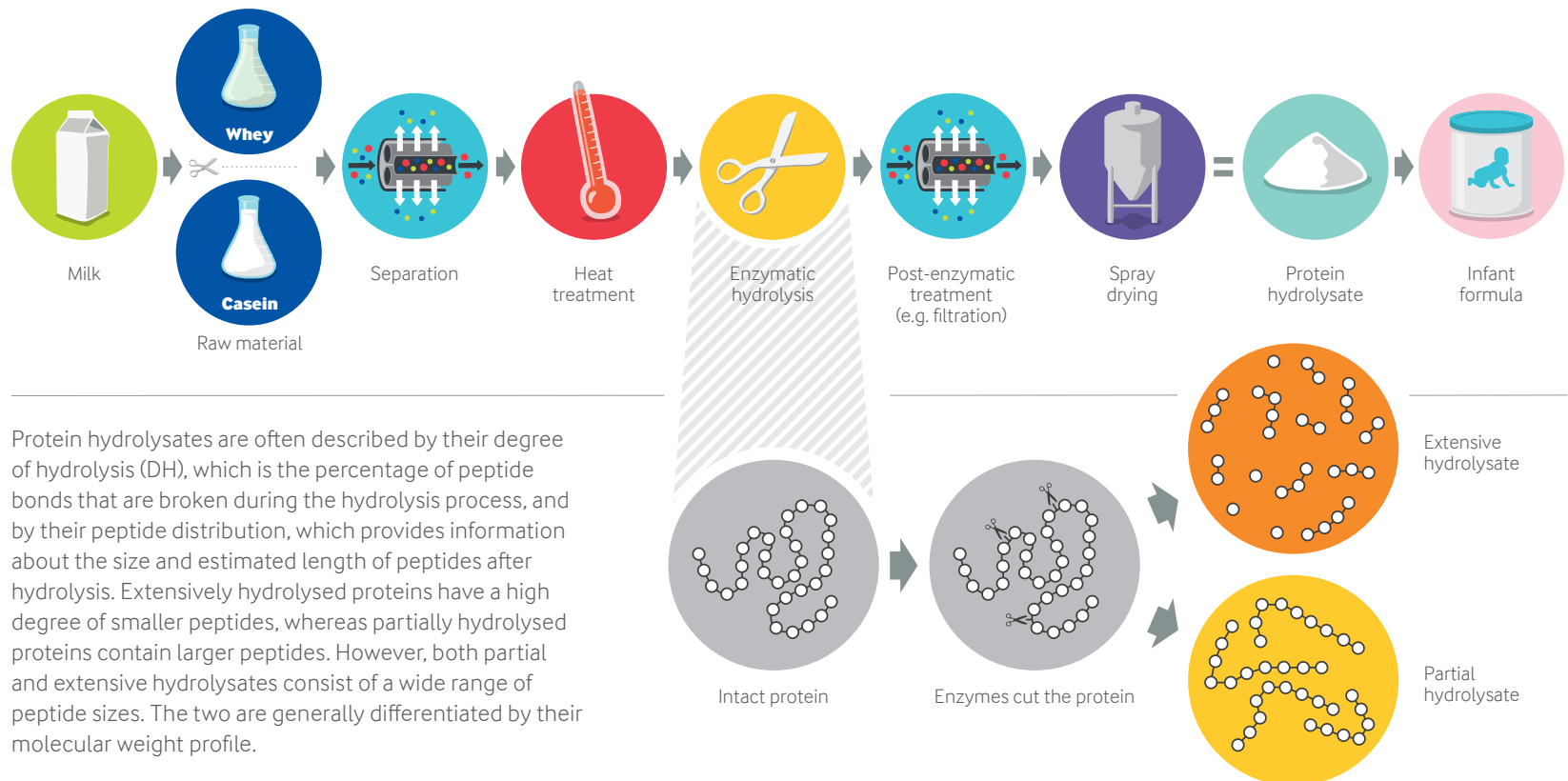
Arla Foods Ingredients
Discovering the wonders of whey 

What is a milk protein hydrolysate?

A milk protein hydrolysate is the result of an enzymatic process, where the intact protein is cut into smaller peptide fragments or free amino acids (figure 1). Industrial enzymatic hydrolysis is similar to the natural breakdown of proteins that takes place in the gastrointestinal system during digestion. For this reason, hydrolysed protein is seen as 'pre-digested'.

Figure 1

Hydrolysis process



Milk protein hydrolysates for allergy management and discomfort reduction

Food allergies, especially in children, are becoming increasingly common in developed and developing countries¹, and current evidence suggests that food allergies affect up to 10% of the population¹⁻³.

On the other hand, up to 30% formula-fed infants often experience gastrointestinal discomfort⁴.

Since their introduction in 1942, milk protein hydrolysates have been widely used in infant nutrition products due to their documented benefits within allergy management and reduction of discomfort.

Arla Foods Ingredients has over 25 years of experience and expertise producing safe and high quality milk protein hydrolysates for the infant formula market. We have state-of-the-art manufacturing facilities, pilot plants, analytical laboratories and R&D facilities for the development and manufacturing of protein hydrolysates.

We invest heavily in pre-clinical and clinical trials, and today we have a range of well-documented milk hydrolysate ingredients with a long history of safe use.

For your next hypoallergenic or comfort infant formula product launch, Arla Foods Ingredients is your trusted partner in your go-to-market journey, offering you support through product development, regulatory and ingredient supply.



Allergy prevalence and manifestations



Worldwide, the prevalence of allergic diseases has continued to rise for more than 50 years⁵.

Among infants, 2-3% suffer from cow's milk allergy, which is one of the most common food allergies in infancy and childhood⁶.

Furthermore, up to 20% of children suffer from atopic dermatitis (AD), and this number is increasing⁷. As the prevalence of allergy and other atopic disorders, such as atopic dermatitis, has grown over the last few decades, strategies to hasten resolution and reduce the incidence have become the subject of increasing focus^{1,7,8}. In most cases, AD appears in the first months of life, and the prevalence decreases around 2-4 years of age. Even though AD is primarily a children's disease, up to 3% of adults are affected^{1,9}.

Anaphylaxis

Irritability

Fussiness

Crying

Respiratory reactions

Rhinitis

Wheezing

Dry cough

Acute asthma

Cutaneous (skin) reactions

Atopic dermatitis

Angioedema

Urticaria (hives)

Gastrointestinal reactions

Enterocolitis

Constipation

Vomiting

Malabsorption

Diarrhea/loose stool



Allergy management with milk protein hydrolysates

For the immune system to elicit an allergic response, it has to recognise epitopes, which are specific parts of the protein. In order to prevent allergic reactions, the epitopes must be destroyed or reduced through hydrolysis (figure 2). Hydrolysed formulas are crucial for the nutrition of infants who are allergic to cow's milk proteins. They are also important for infants identified as being in the allergy risk group, where allergy management is required¹⁰⁻¹².

Extensive hydrolysates

Extensive, filtered hydrolysates, where almost all epitopes have been destroyed (figure 2), contain significantly reduced levels of potential allergens. This makes them ideal for hypoallergenic formulas for infants with a cow's milk allergy (CMA) diagnosis or as a preventive formula for high-risk infants.

Extensive hydrolysates are classified as having peptides with a molecular weight of generally <3000 Da, where the majority are below 1500 Da¹³⁻¹⁵.

Cow's milk-based extensively hydrolysed formula with a proven efficacy (tolerated by more than 90% of patients with CMA) remains the recommended and preferred therapeutic choice for infants with CMA, while amino acid formulas are reserved for the most severe cases^{16,17}. Soy protein-based formulas are not recommended for infants younger than 6 months¹⁷.

Partial hydrolysates

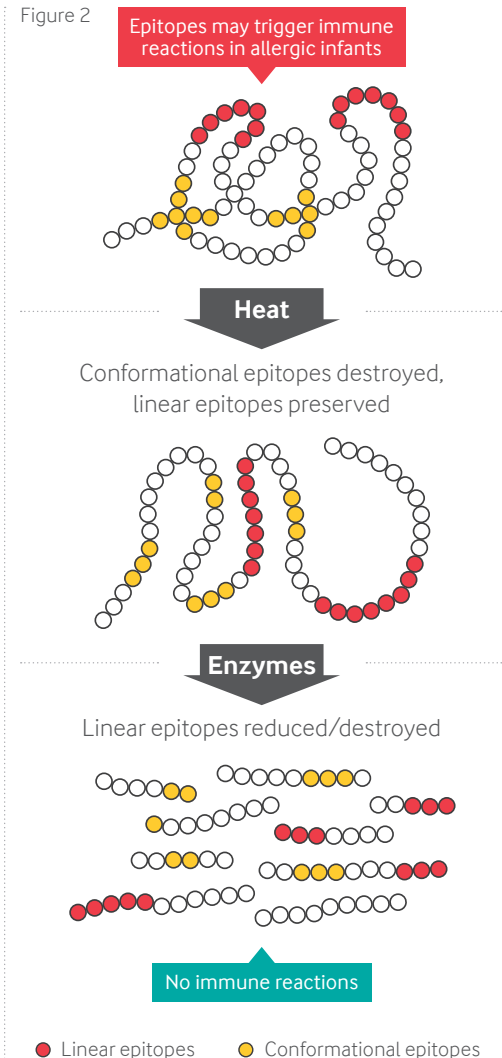
In partially hydrolysed proteins, some epitopes and hereby allergens are still present, providing the potential to stimulate oral tolerance. Exposure to allergens is critical in order to build oral tolerance towards normal food components that the infant will consume in later life. It is argued that partially hydrolysed proteins may be a good choice for allergy prevention in high-risk infants because of the possible induction of oral tolerance¹⁸.

Partial hydrolysates are classified as having peptides with a molecular weight of generally <5000 Da, but with ranges between 3-10 kDa^{3-15,19,20}.

Linear epitopes – amino acid residues (8-15) are adjacent in the polypeptide chain that might trigger an immune response

Conformational epitopes – created from amino acid residues located in different parts of the polypeptide chain

Figure 2



Documented benefits of whey protein hydrolysates for allergy management

Strategies for allergy management in infants

Breastfeeding should be encouraged as the best way to feed infants. However, if breastfeeding is not possible, hydrolysed formulas with a clinical proof of efficacy are recommended for infants with allergy^{16,21,22} (figure 3).

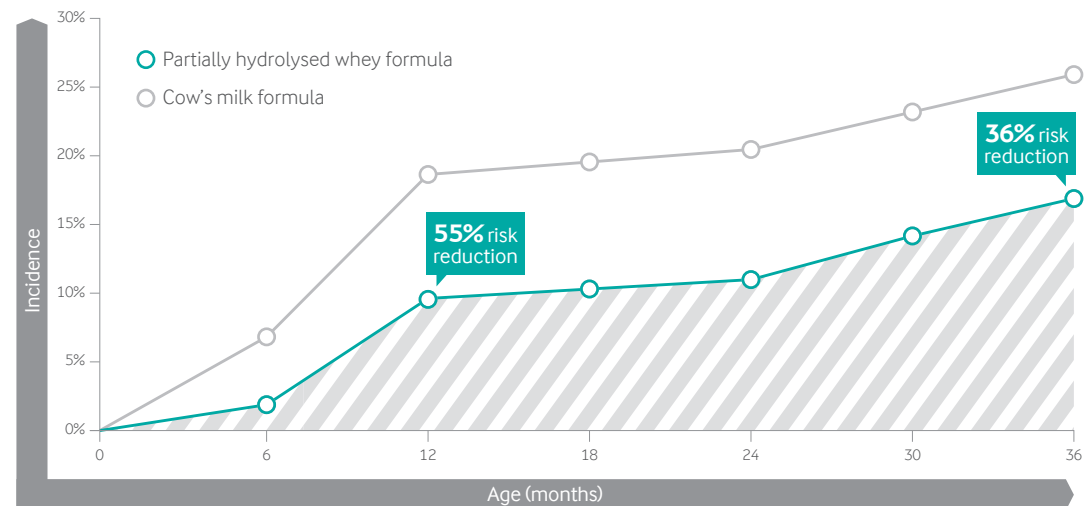
Figure 3



Allergy management – prevention

Clinical studies have observed reduced risk of atopic dermatitis among infants fed hydrolysed infant formulas compared with infant formulas based on intact proteins^{11,23}. A meta-analysis has shown that prolonged feeding with partially hydrolysed formula reduced the incidence of AD in healthy, high-risk infants with allergies in the family by 55% compared to infants fed with intact protein¹¹ (figure 4).

Figure 4



As 50% of the infants that develop an allergy do not fall into the high-risk category, scientists have been looking into how partially hydrolysed whey formulas (pHF-w) would affect infants in the general population in regard to allergic manifestations and growth. In five studies, using the same pHF-w, the effect was still seen after correcting for the allergy risk. Hence, when breastfeeding is not possible, feeding a specific pHF-w instead of intact cow's milk formula (CMF) may reduce the risk of AD in the general infant population while still supporting age-appropriate growth²⁴.

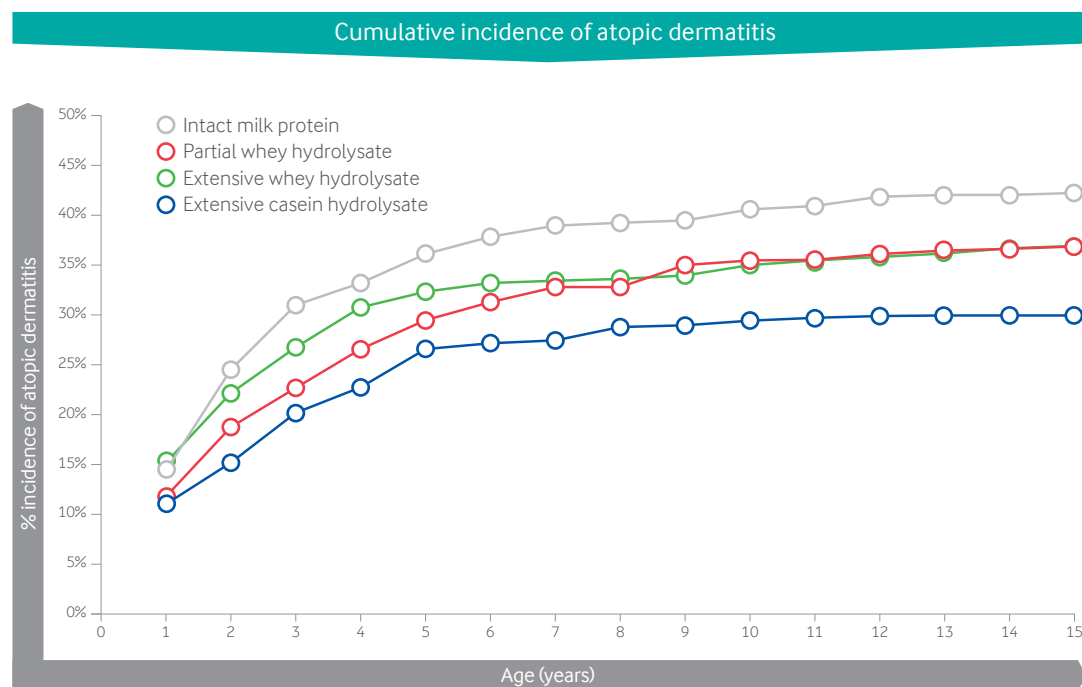
In the German GINI study (German Infant Nutritional Intervention study) four formulas were tested in a randomised, double-blinded clinical set up on high-risk infants (n=998) – partial whey hydrolysate, extensive whey hydrolysate, extensive casein hydrolysate and intact milk protein. The infant formulas were given as the only substitute to breast milk for the first four months of life. The study reported a significant risk reduction of AD up to 15 years of age – especially for infants receiving the extensively hydrolysed casein¹⁰ (figure 5). A very important finding of the GINI study was that it was impossible to predict the effect based on protein source and degree of hydrolysis. Hence, it makes sense that every hydrolysed formula needs its own clinical study to show efficacy in reducing the risk of allergic manifestations (according to the EU regulation)²⁵.

Studies on Arla Foods Ingredients hydrolysates

In an infant clinical study, 106 high-risk infants were divided into two groups. A breastfed group and a group receiving hypoallergenic (HA) formula based on the extensive whey hydrolysate Peptigen® IF-3080. There were no significant differences regarding the development of atopic dermatitis (SCORAD) between the groups in the first two years of life. Furthermore, there were no differences in measured immunological outcomes (IgE/IgG and cell reactivity to beta-lactoglobulin (BLG)) between the groups. It was concluded that a HA-formula based on Peptigen® IF-3080 secured proper growth and provided atopic levels similar to breastfeeding²⁶⁻²⁷.

Peptigen® IF-3080 has also been part of a study where the primary endpoint was non-inferiority of daily weight gain during the first four months of life compared to regular formula. The study was performed in 402 healthy term infants, and Peptigen® IF-3080 proved safe and suitable²⁸.

Figure 5



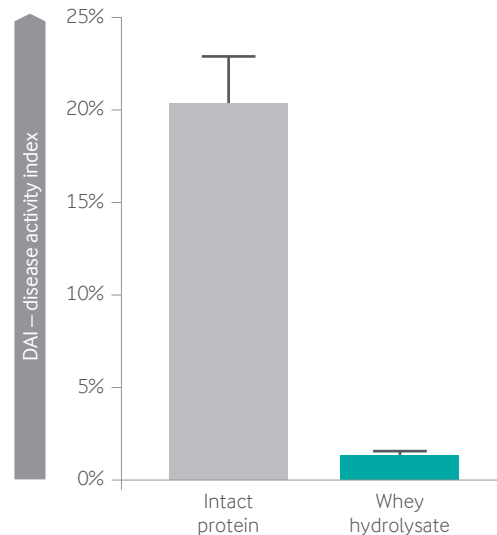
Pre-clinical studies on Arla Foods Ingredients hydrolysates

Oral tolerance is the consequence of a systemic absence of a response to a dietary antigen²⁹. Animal studies have shown that partial hydrolysates are able to induce oral tolerance to intact proteins, whereas extensive hydrolysates are not³⁰. Induction of oral tolerance by peptides derived from milk is a powerful measure to pull the immune system towards tolerance instead of sensitisation.

A Brown Norway rat model has been developed to measure how different milk-based hydrolysates will have an impact on the immune system in regard to sensitisation and induction of tolerance³¹. The model showed that intact BLG was the most efficient in prevention of sensitisation, followed by partial hydrolysate (Lacprodan® IF-3087), whereas extensive hydrolysate (Peptigen® IF-3080) only showed an insignificant preventive capacity³².

However, Peptigen® IF-3080 has been shown to prevent development of allergic manifestations in sensitised mice. BALB/c-mice were sensitised to beta-lactoglobulin (BLG) and challenged with intact whey or hydrolysed whey, where after allergic and immunological properties were measured. The study showed that consumption of Peptigen® IF-3080 prevented clinical signs of allergy in mice, suggesting that Peptigen® IF-3080 may be safely used for already sensitised infants³³ (figure 6).

Figure 6



Allergy management – treatment

If breastfeeding is not possible, the recommended diet for an infant with CMA is an extensively hydrolysed infant formula with proven efficacy (tolerated by more than 90% of patients with CMA)³⁴⁻³⁹. Only infants with extremely severe allergic symptoms are recommended AAF (free amino acids with no peptides) as the first choice. Soy protein-based formulas may only be an option in infants older than 6 months¹⁷.

NASPGHAN and ESPGHAN recommend that soy formula should not be used in infants with food allergy younger than 6 months^{40,41}.

“Soy protein has no role in the prevention of allergic diseases and should not be used in infants with food allergy during the first 6 months of life”¹⁷.

Formulas with milk from other mammalian species (sheep, buffalo, horse, camel or goat) or unmodified soy or rice drink should not be used to treat CMA because of a high rate of possible allergenic cross-reactivity and insufficient nutritional value³⁴. Furthermore, plant-based drinks are not recommended because of their nutritional inadequacy⁴².

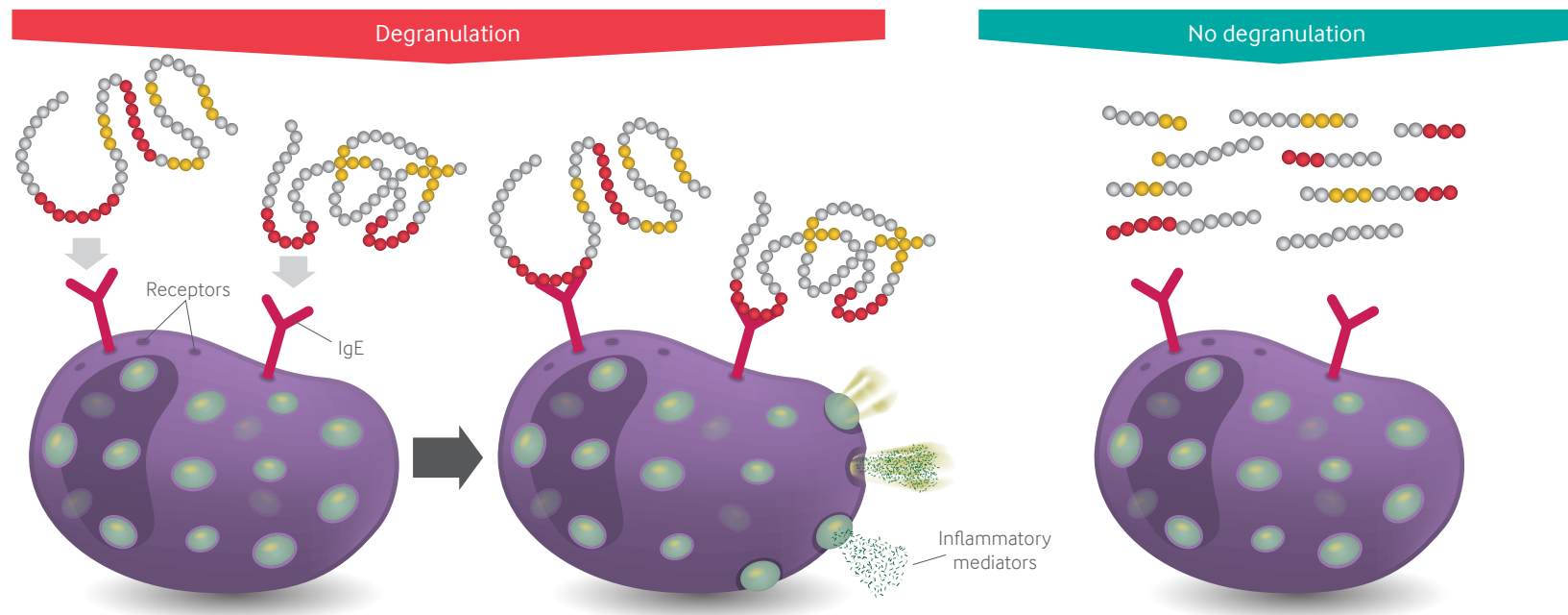
Infant clinical studies are the only real validation of hydrolysates in regard to allergenicity. However, an *in vitro* model, the RBL (rat basophil leukemia) assay, has been widely used for predicting and determining residual allergenicity of hydrolysates⁴³. The assay is an optimal approach to investigate allergenic potential of food proteins, in an easy-available, sensitive, specific and reproducible set-up.

RBL cells are sensitised with a pool of chimeric antibodies directed against BLG⁴⁴. The antibodies can bind to epitopes from the hydrolysate, resulting in crosslinking on the surface of the cells, leading to degranulation (figure 7). Hence, if the cells degranulate, the hydrolysate will have an allergic potential, whereas if no degranulation is seen, the hydrolysate will not have any residual allergenicity.

Whey hydrolysates are added to the RBL assay, after which degranulation is determined and can be measured as a sign of residual allergenicity (in μg BLG/g protein). Results less than 10 μg BLG/g protein can be interpreted as “no residual allergenicity left”, meaning the hydrolysate can be suitable for allergic infants.

Peptigen® IF-3080, Peptigen® IF-3090 and Peptigen® IF-3032 showed values below 10 μg BLG/g protein.

Figure 7



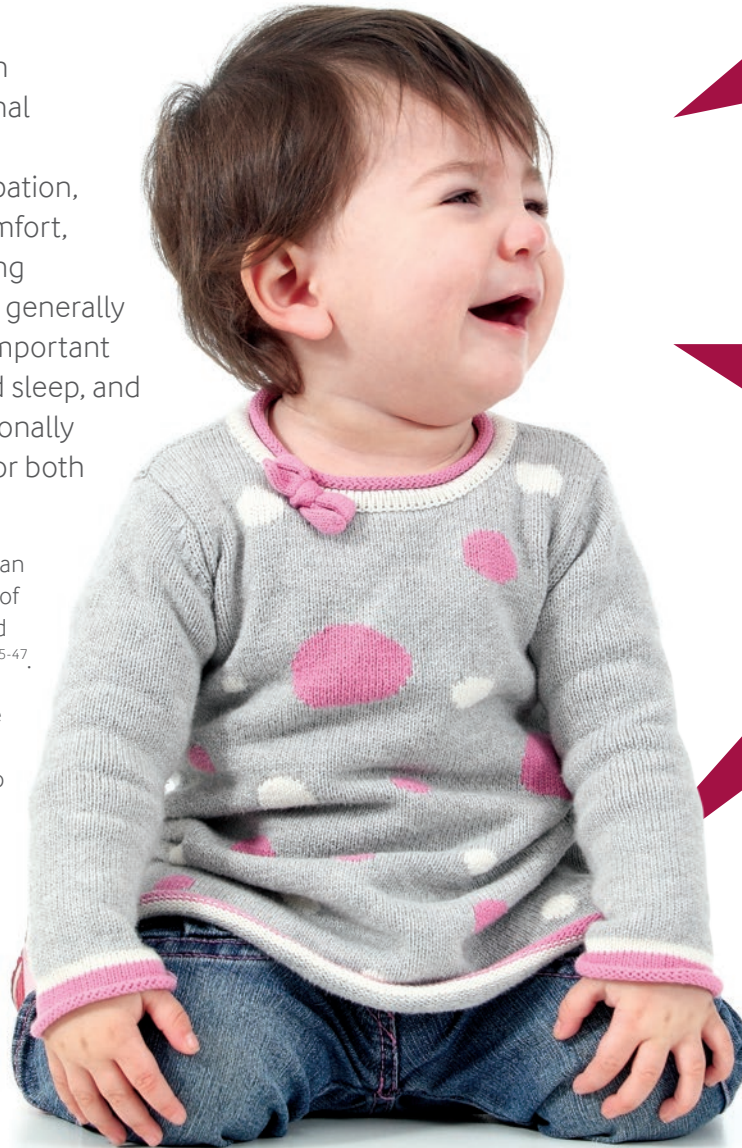


Infant gut discomfort

Formula-fed infants often experience gastrointestinal discomfort such as colic, regurgitation and constipation, leading to general discomfort, poor sleep and long crying intervals⁴. Gut comfort is generally regarded as being very important to infants' well-being and sleep, and discomfort can be emotionally and physically draining for both infants and parents.

There is evidence that crying can trigger premature termination of breastfeeding, overfeeding and poor parent-child relationship⁴⁵⁻⁴⁷.

Infant discomfort problems are the most common reasons for why parents switch formulas to find a solution to their infant's gastrointestinal issues⁴⁸.



Excessive crying

Infant crying is a part of normal development, but excessive crying (more than 1½-2 hours per day⁴⁹) in healthy infants is known as colic. Colic affects approximately 20% of infants worldwide⁴ and is one of the most common problems in early infancy⁴⁶.

Excessive regurgitation

Regurgitation is the involuntary return of swallowed food or secretions into or out of the mouth and should be distinguished from vomiting⁵⁰. In most cases, regurgitation is considered normal, but episodes twice or more per day can be a problem. The prevalence of this condition is 30% worldwide⁴.

Stool issues

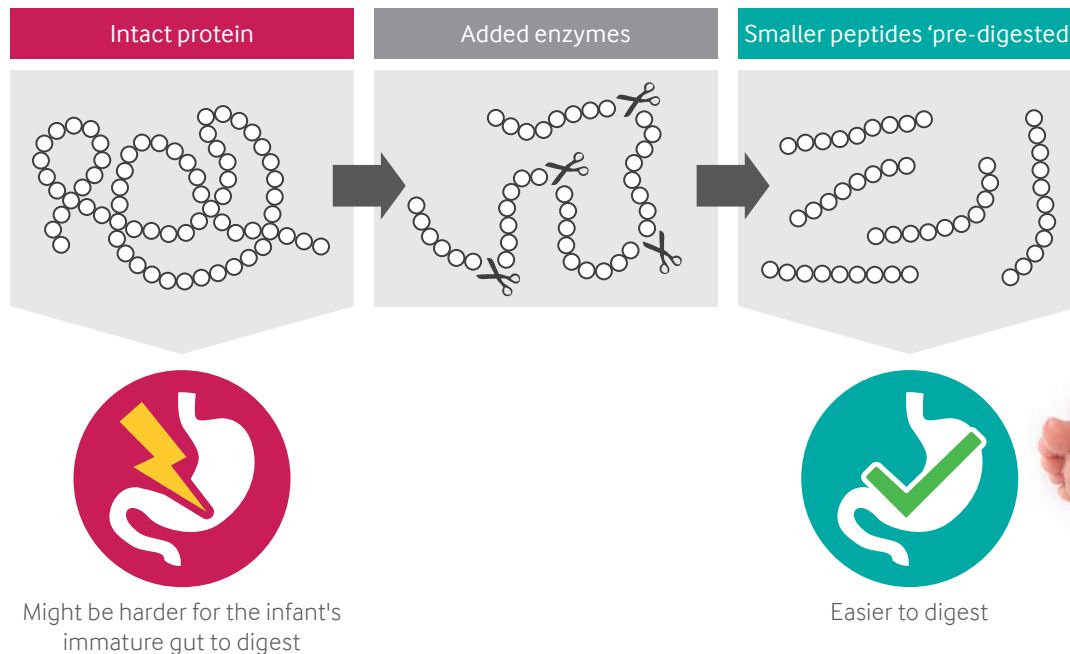
Formula-fed infants have less frequent and more solid stools compared to breastfed infants. Hard stools leading to pain, constipation and crying are found in 1.1% of breastfed infants versus 9.2% in formula-fed infants⁵¹. Constipation, the opposite of diarrhoea, is a common problem during childhood with an estimated prevalence of 30%⁵².

Comfort with milk protein hydrolysates

Infant formulas contain much more protein (40-50%) than human milk⁵³. As protein is difficult to digest for the immature infant gastrointestinal system, it can result in discomfort for the infant⁵⁴. By altering the amount and type of proteins in infant formulas, it is possible to reduce gastrointestinal discomfort (figure 8).

Studies have shown that uptake of smaller peptides, as in protein hydrolysates, is faster than the uptake of free amino acids or intact protein. Potentially, this could lead to improved comfort for the infants⁵⁵⁻⁵⁷. The use of hydrolysed milk protein in infant formulas has been demonstrated to have a beneficial effect on infants with colic^{58,59} and can also improve stool consistency⁶⁰ compared to a standard infant formula^{61,62}.

Figure 8



Documented benefits of protein hydrolysates for gut comfort

Gastrointestinal symptoms are very common in infants <12 months of age and may impact on future health problems⁴. For infants with gastrointestinal problems, some evidence suggests that using hydrolysed formulas may be beneficial^{58,63}.

Hydrolysed formulas show a significantly higher availability of smaller peptides and less intact protein than standard formulas based on intact protein. Already pre-digested, hydrolysed formulas may improve the digestibility.

A double-blinded, randomised cross-over intervention trial with a standard formula (intact protein) versus formulas based on partial and extensive hydrolysate respectively, clearly showed that the extensive hydrolysate reduced gastric emptying time⁶⁴. The use of an infant formula that supports faster gastric emptying may improve feeding tolerance, especially in sensitive groups of infants.

In another double-blinded, randomised, placebo-controlled trial, infants with colic were fed either an extensive whey hydrolysate formula or a standard formula. When adjusted for confounders, crying among infants fed the whey hydrolysate formula was reduced by 63 minutes a day⁵⁹.

In two recent studies^{62,65}, it was shown that partially hydrolysed formulas were able to induce significantly softer stool and fewer hard and formed stools than standard infant formula (figure 9 and 10). One of the studies also showed a reduced incidence of episodes with colic (figure 11).

It has been suggested that partial whey hydrolysed formula may offer a useful alternative to intact protein in the dietary management of common functional gastrointestinal symptoms¹⁴.

Figure 9

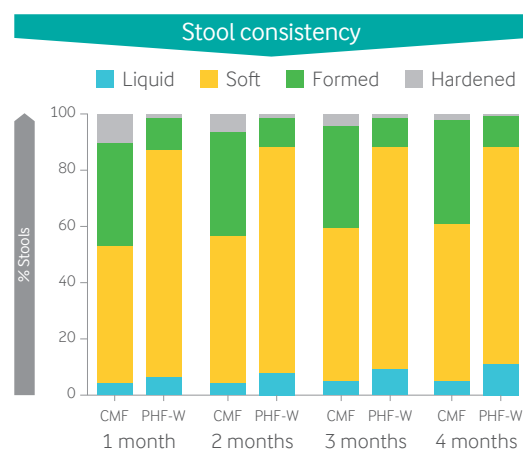


Figure 10

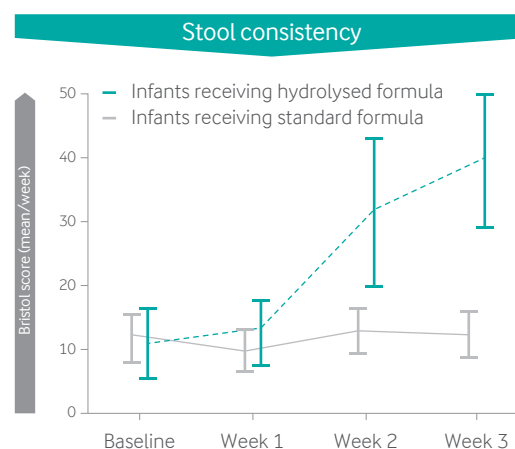
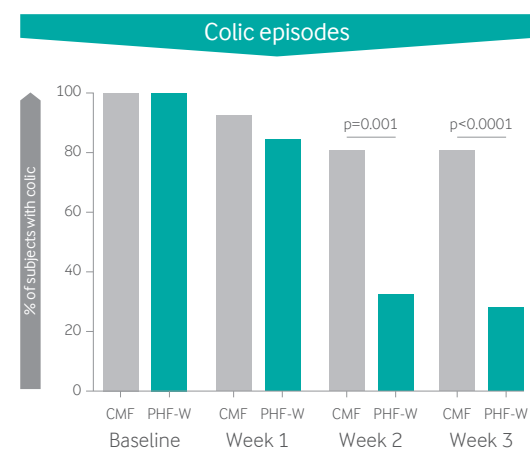


Figure 11



Milk protein hydrolysate formula market



Between 2014 and 2018, global infant and baby formula product launches with whey protein hydrolysates (WPH) increased 7.9% CAGR⁶⁶ (figure 12), with West Europe, Asia and East Europe as the regions with more product launches.

During the same period of time, global baby formula product launches positioned for allergy management and comfort/easy-to-digest have increased 5.3% CAGR and 7.8% CAGR, respectively (figure 12).

In regards to shopper awareness of whey protein hydrolysates, a global consumer study revealed that 32% of mothers claimed to know this ingredient, 31% of the group claiming to be familiar with it also expressed a preference for an infant formula containing this ingredient⁶⁷ (figure 13).

In hypoallergenic formulas, whey protein hydrolysates are typically communicated as proteins that have been broken down into smaller pieces, which reduces the risk of the infant developing an allergic response. On the other hand, in formulas positioned as comfort/easy-to-digest, whey protein hydrolysates are communicated, for instance, as “partially digested proteins”, “gently split proteins”, or “protein that is soft on the stomach, facilitating its absorption”.

Figure 12

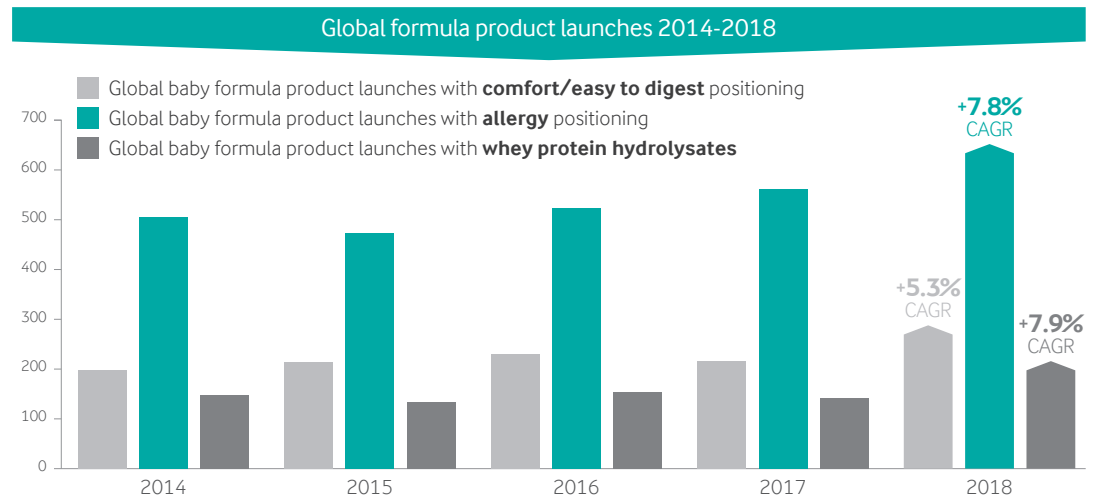
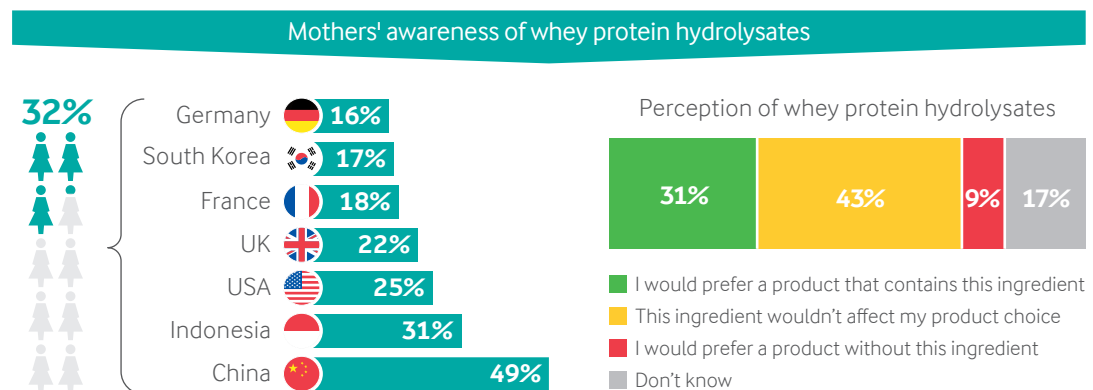
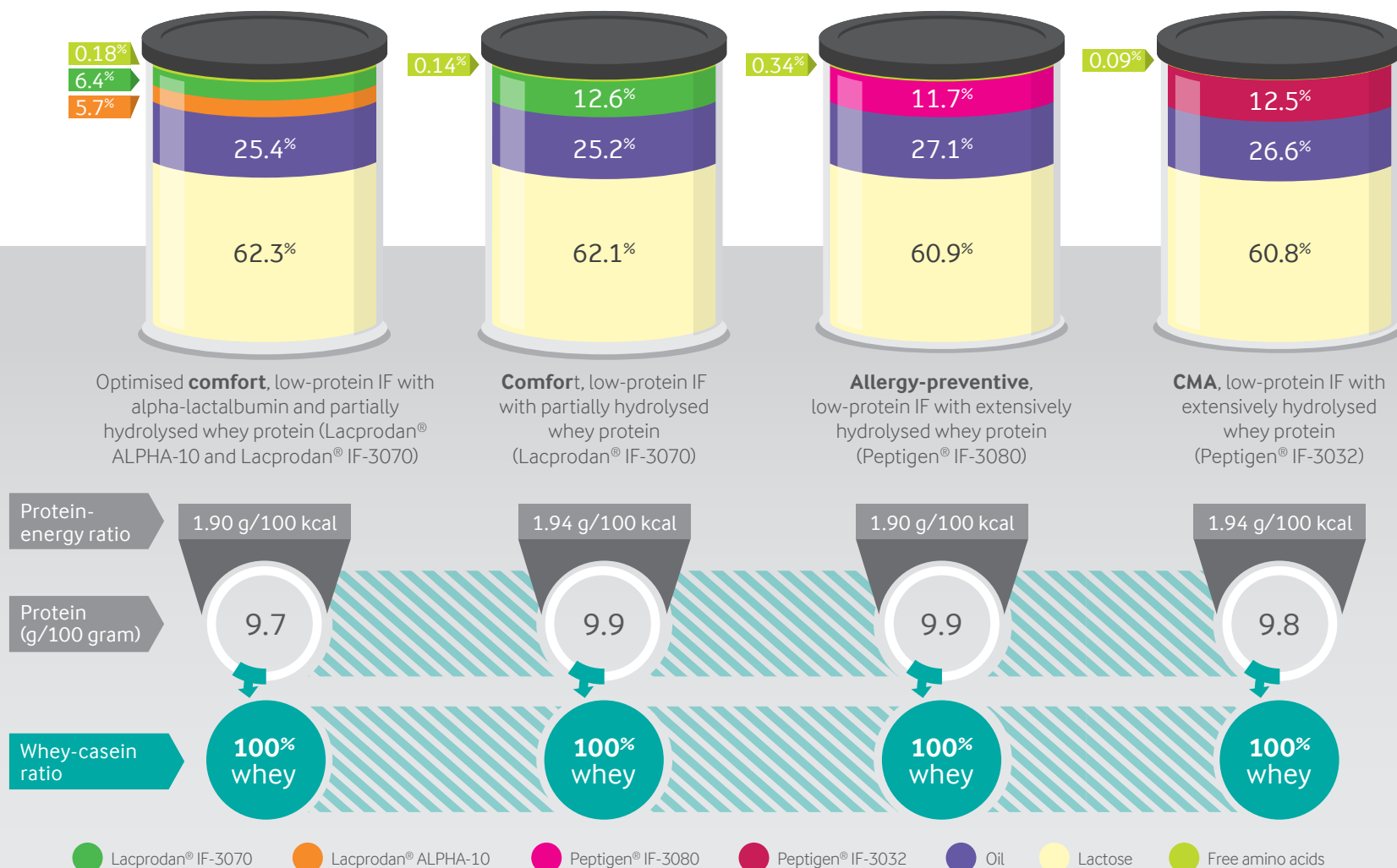


Figure 13





Our suggestions for formulations with whey protein hydrolysates



Arla Foods Ingredients' milk protein hydrolysate product range



								
Protein source 	100% whey	100% whey	100% whey	100% whey	100% whey	100% whey	100% whey	100% casein
Degree of hydrolysis 	25-30%	25-30%	21-28%	18-20%	9-15%	7-12%	7-12%	6-10%
Protein content 	min. 83%	min. 85%	min. 70%	min. 77%	min. 76%	min. 76%	min. 52%	min. 88%
Lactose content 	max. 4.5%	max. 0.2%	max. 3%	max. 0.5%	max. 3%	max. 3%	max. 33%	max. 0.3%
Recommended use 	Infant allergy management	Infant allergy management	Infant allergy management FSMP	Infant allergy management Infant comfort	Infant comfort	Infant comfort	Infant comfort	Mineral absorption Infant comfort CPP nutrient fortifier in China
Available documentation 	Clinical studies, RBL-assay	RBL assay	RBL assay	Animal study				Animal study
Regulatory compliance (composition and production) 								

Hydrolysate capabilities at Arla Foods Ingredients

A world leader in hydrolysate production

- More than 25 years of experience in milk-derived protein hydrolysate production
- Broad milk and whey-derived protein hydrolysate portfolio
- Opportunities for customised protein hydrolysate
- State-of-the-art manufacturing facilities, pilot plants, analytical laboratories and R&D facilities

New hydrolysate facility at our Danmark Protein plant

- Complies with the strictest quality and safety standards
- Annual capacity of 4,000 tonnes
- Dedicated packaging line for filtered products

Premium quality hydrolysate ingredients

- Scientifically documented
- Excellent solubility and taste
- Excellent microbiology
- Uniform quality
- Kosher and Halal approved
- Controlled prevention of allergen cross-contamination

Frontrunners in research and development of hydrolysates

- Extensive clinical study experience
- Broad scientific network
- Support for following the new global legislation regarding IF for allergic prevention. Including new EU regulations and the new GB 25596-2010 standard on FSMP in China.





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Why choose Arla Foods Ingredients?

Among the top world manufacturers of natural whey solutions

- Among the world's largest producers of whey protein hydrolysates, MFGM, whey protein isolates, whey protein fractions and lactose
- Producing whey proteins since 1980
- State of the art production plant with possibilities to customise ingredients

R&D in our DNA

- Over 15% of our employees in Denmark work in R&D
- Collaboration with top universities worldwide
- Clinical and scientific documentation
- Application centres in two continents

Premium quality by design

- Our factories adhere to the strictest quality and safety standards
- Premium quality ingredients
- Kosher and Halal certification
- Free of annatto
- Non-GMO
- Vegetarian

Your trusted business partner

- Application support
- Business development support
- In-depth nutrition research and formulation support
- Technical know-how to implement products in customer's product line

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Arla Foods Ingredients

Discovering the wonders of whey