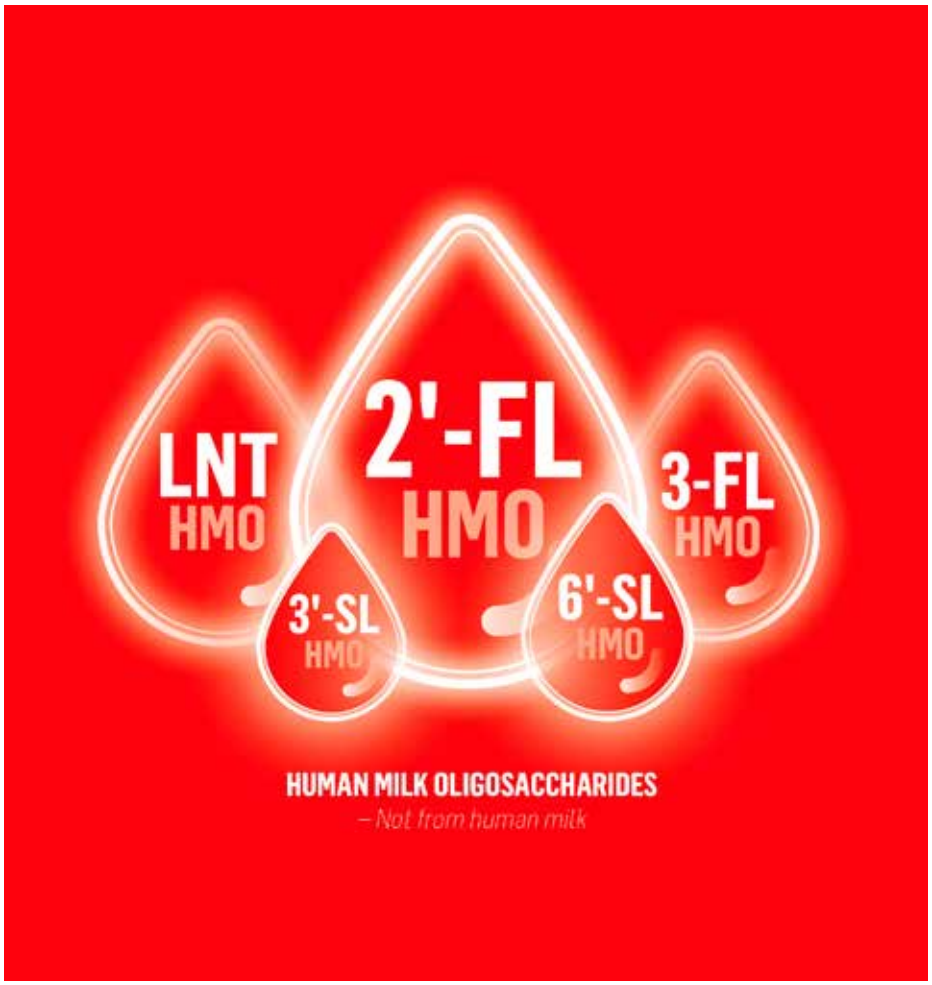
Functional sugars in their diversity

Jennewein will be offering HMO mix for baby food in near future.

Jennewein Biotechnologie GmbH in Rheinbreitbach specializes in the development of innovative production processes for rare and functional sugars. The focus here is particularly on the development of efficient production processes and the production of rare monosaccharides and complex oligosaccharides, which have proven health benefits. The company has proved, among other things, to be a pioneer in the industrial production of human milk oligosaccharides (HMOs), which naturally only occur in breast milk.

Since Jennewein Biotechnologie GmbH was founded in Rheinbreitbach in 2005, the company has followed an unprecedented road to success. The success began with the development of efficient, industrial processes for the production of human milk oligosaccharides, which are otherwise only found in breast milk – a biotechnology process that up until this point was considered absolutely impracticable. These complex sugar molecules can be defined as deconjugated, complex glycans, composed of various monosaccharide subunits, specifically glucose, galactose, L-fucose, N-acetylneuraminic acid and N-acetylglucosamine. In terms of structure, diversity and concentration, they are found exclusively in human milk. They have well-documented health benefits such as a prebiotic effect and the promotion of the development of a healthy gut microbiome in children and adults.

For production, the biotechnology experts use a self-developed process based on bacterial fermentation. The first product was 2`-fucosyllactose (2`-FL), the most common HMO found in breast milk. In an efficient fermentation process, more than 10 tons of 2‘-FL can be obtained, most of which is used in baby food. The product is distributed worldwide, with a special focus on the USA and the EU. In addition to the main baby food segment, the medical



Closer to breast milk than ever before: The 5 HMO mix will be the first product worldwide to contain both neutral and acidic HMOs, thus combining a multitude of the positive effects of different HMOs in one product. (photograph: Jennewein Biotechnologie GmbH)

nutrition sector is also targeted. There are other applications, especially for monosaccharides such as L-fucose and sialic acid, in the pharmaceutical and cosmetics industries.

In addition to the development of new and efficient production processes for rare functional sugars, the company also cooperates with selected partners in the field of preclinical, safety and toxicological studies. The main objectives are to examine the health-related properties of the sugar produced in-house and to deal with important safety and toxicological issues with regard to the use of the products.

Now also HMO mix on offer

The success of the first products was an incentive for the Rheinbreitbach company to further expand their range. With the introduction of the 5 HMO MIX containing the five most common HMOs – 2`-FL, 3-fucosyllactose (3-FL), lacto-N-tetraose (LNT), 3`sialyllactose (3`-SL) and 6`-sialyllactose (6`-SL) – the next generation of HMO products will soon be launched on the market. In order to achieve approval in the various regions, a few hurdles still had to be overcome.

At the beginning of the year, another milestone in the worldwide approval of this new product generation, the "5 HMO mix," was achieved. The data from a toxicological study by the company were accepted for publication by the renowned specialist journal "Food and Chemical Toxicology" for publication under the title "A Safety Evaluation of Mixed Human Milk Oligosaccharides in Rats."

The HMO mix consists of the five mentioned HMOs. The results show that the consumption of the HMO mix is well tolerated and harmless, even in high doses. The study was carried out in accordance with the internationally recognized OECD guidelines.

Proof of the harmlessness of the product was also a prerequisite for the "Growth and Tolerance" study currently being carried out by Jennewein Biotechnologie. In this study, baby food with the HMO mix is used in a concentration that is similar to that of the individual HMOs in breast milk. One aspect of this clinical study is the evaluation of the positive effects of the HMOs on the intestinal microbiome of the participating babies in comparison to a control group that consumed conventional baby food or a group of breastfed children. "After Jennewein Biotechnologie introduced 2'-fucosyllactose into the baby food market for the first time in 2015, a revolution in the baby food market is in sight with the commercialisation of the HMO mix and its use in natural concentrations," says CEO Dr Stefan Jennewein. "By supplementing with HMOs in the natural concentration, artificial prebiotics such as GOS and FOS can be completely replaced," is his conclusion.

The 5 HMO mix will be the first product worldwide to contain both neutral and acidic HMOs and thus combines a large number of the positive effects of different HMOs in one product.

Anti-infective effects

According to other study results, all HMOs in the mix show anti-infective effects against a variety of pathogens such as campylobacter jejuni (2'-FL), salmonella (2'-FL, 3-FL), streptococci (LNT), noroviruses and rotaviruses (2'-FL, 3-FL, 3'-SL and 6'-SL).[1] They help to build a natural intestinal microbiome, as they lead to a multiplication of useful bacteria such as bifidobacteria, lactobacilli and bacteroides.[2, 3, 4] 2'-FL, 3-FL and 6'-SL support intestinal health by promoting intestinal motility and the maturation of the intestinal epithelial cells.[5, 6]

In addition, sialyzed and fucosylated HMOs (2'-FL, 3-FL, 3´-SL and 6'-SL) have an immune-regulating effect. In children who are not breastfed, they normalize the level of cytokines and inflammation markers and thus contribute to an improvement in the Th1 / Th2 balance.[7] 3'-SL and 6'-SL in particular promote the development of the baby's brain by providing sialic acid, an essential component for neurons.

In many animal models, supplementation with sialic acid and sialyllactose was associated with better learning and memory performance. The company not only offers these HMOs in the greatest variety, but also in natural concentrations. The new generation of product will thus help to bring baby food even closer to the natural state of breast milk. The HMO mix will be produced in Rheinbreitbach on an industrial scale under FSSC 22000 and ISO 9001. The product will be offered as spray-dried powder.

Research activities are being further expanded

The company's research activities with regard to HMOs are far from over. "We are currently working on the development of the next generation of human milk oligosaccharides. These are fucosylated pentaoses, e.g., lacto-N-fucopentaose I," explains Dr Katja Parschat, Deputy Head of Research and Development at Jennewein Biotechnologie GmbH. "For these HMOs, some of which are also found in higher concentrations in breast milk, in addition to their prebiotic effectiveness, positive effects in protection against norovirus infections have also been proven in some cases. The aim is to produce more HMOs in order to keep getting closer to the HMO profile in breast milk." In addition, the formation of bacterial metabolites released by intestinal bacteria that metabolize HMOs is currently being investigated. These metabolites such as short-chain fatty acids are known for their positive properties, e.g., the maturation and stability of the intestinal epithelium.

The activities are supported by a new research and development centre in Bonn, which is almost completed. In particular, the development of new production lines will to be promoted there. In addition, new designer microorganisms are to be developed there using molecular genetic methods, which will represent the next level of "cell factories" for the production of complex oligosaccharides.

1. Triantis V et al. Immunological Effects of Human Milk Oligosaccharides. Front Pediatr 2018; 6: 190
2. Thurl S. et al. Systematic review of the concentrations of oligosaccharides in human milk. Nutr Rev. 2017; 75: 920-933
3. Yu Z et al. Utilization of major fucosylated and sialyated human milk oligosaccharides by isolated human gut microbes. Glycobiology 2013; 23: 1281-1292
4. Thongaram T et al. Human milk oligosaccharide consumption by probiotic and human-associated bifidobacteria and lactobacilli. J Dairy Sci. 2017; 100: 7825-7833
5. Bienenstock J et al. Fucosylated but not sialylated milk oligosaccharides diminish colon motor contractions. PLoS ONE 2013, 8:e76236
6. Holscher et al. Human Milk Oligosaccharides Influence Intestinal Epithelial Cell Maturation In Vitro. J Pediatr Gastroenterol Nutr. 2017; 64(2):296-301
7. Xiao et al. Human milk oligosaccharides promote immune tolerance via direct interactions with human dendritic cells. Eur J Immunol. 2019, 49(7):1001-1014
8. Wang B et al. Dietary sialic acid supplementation improves learning and memory in piglets. Am J Clin Nutr. 2007;85(2):561-9
9. Jacobi SK et al. Dietary Isomers of Sialyllactose Increase Ganglioside Sialic Acid Concentrations in the Corpus Callosum and Cerebellum and Modulate the Colonic Microbiota of Formula-Fed Piglets. J Nutr. 2016;146(2):200-8