APPLICATION FOR THE APPROVAL OF THE HUMAN-IDENTICAL MILK OLIGOSACCHARIDE 3'-SIALYLLACTOSE SODIUM SALT AS A NOVEL FOOD INGREDIENT FOR USE IN INFANT AND FOLLOW-ON FORMULAE AND IN FOODS

Regulation (EU) No 2015/2283 of the European Parliament and of the Council of 25 November 2015 Concerning Novel Foods and Novel Food Ingredients

Non-Confidential Summary of the Application

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Summary

The subject matter of this application is 3'-sialyllactose sodium salt (3'-SL), which is obtained from fermentation and is isolated as a purified ingredient in the sodium salt form. 3'-SL is a trisaccharide made from glucose, galactose and *N*-acetylneuraminic acid (NANA, also known as "sialic acid"). Glucose and galactose comprise the milk sugar lactose and NANA is an acidic monosaccharide (approved as a novel food ingredient in its own right for use in a variety of foods including infant and follow-on formula[1]). The manufactured 3'-SL is identical in structure to the same molecule that is present in human milk and is therefore henceforth referred to as human-identical milk oligosaccharide (HiMO)[2]. 3'-SL is one of the most abundant sialylated (acidic) individual oligosaccharides of the complex natural oligosaccharide fraction of human milk. There are 2 naturally occurring sialyllactoses, namely 3'-SL and 6'-sialyllactose (6'-SL), which are regio-isomers (*i.e*. the NANA moiety is connected to another position of lactose). Both sialyllactoses share common functions and biological roles, with some subtle differences.

Glycom's 3'-SL ingredient is manufactured and purified in several steps to a well-defined and highly pure specification, containing not less than 90.0 % human-identical milk saccharides (HiMS) [predominantly 3'-SL (≥88 %), with some levels of lactose (the principal raw material) and NANA]. In stage 1 of the manufacturing process (upstream processing), D-lactose and D-glucose are converted to 3'-SL by the adapted cellular metabolism of the 3'-SL production microorganism, which uses glucose as an energy and carbon source and lactose as a substrate for 3'-SL biosynthesis. In stage 2 (downstream processing), a series of purification and isolation steps are used to generate the final 3'-SL ingredient in the sodium salt form.

The 3'-SL ingredient is intended for use in food and beverages targeted towards older population groups (up to 0.25 g/L or 2.5 g/kg), foods for special medical purposes (use level determined on a case-by-case basis), foods for total diet replacement for weight control (up to 0.5 g/L or 5 g/kg), and supplements (0.5 g/day in the general population). The maximum use levels are proposed on the basis of providing similar levels of 3'-SL as those occurring on average in mature human breast milk, and have been balanced for other age groups as well to achieve resulting intakes that stay well within the natural intakes from breast milk on a body weight basis.

Table 1 Proposed Food Uses and Use Levels for 3'-SL

EU Food Category Number[a]	Food Category Name	Proposed Maximum Use Level
1	**Dairy products and analogues**	
1.1	Unflavoured pasteurised and unflavoured sterilised (including UHT) milk	0.25 g/L
1.2/1.3	Unflavoured fermented milk-based products	0.25 g/L beverages
		2.5 g/kg products other than beverages
1.4	Flavoured fermented milk-based products including heat-treated products	0.25 g/L beverages
		2.5 g/kg products other than beverages
7	**Bakery wares**	
7.2	Fine bakery wares. Cereal bars only	2.5 g/kg
13	**Foods for Special Groups (FSG)**	

[1] Commission Implementing Regulation (EU) 2018/1023 of 23 July 2018 correcting Implementing Regulation (EU) 2017/2470 establishing the Union list of novel foods. https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1532967158300&uri=CELEX:32018R1023

[2] Throughout this application, the term "human milk oligosaccharide (HMO)" is used to refer to the naturally occurring oligosaccharides in human breast milk, while the term "human-identical milk oligosaccharide (HiMO)" is used to refer to the manufactured counterparts of these substances.

Table 1 Proposed Food Uses and Use Levels for 3'-SL

EU Food Category Number[a]	Food Category Name	Proposed Maximum Use Level
13.1	**Foods for infants and young children**	
13.1.1	Infant formula as defined in Regulation (EU) No 609/2013	0.2 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
13.1.2	Follow-on formula as defined in Regulation (EU) No 609/2013	0.15 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
13.1.3	Processed cereal-based food and baby food for infants and young children as defined in Regulation (EU) No 609/2013	0.15 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
		1.25 g/kg for products other than beverages
13.1.4[b]	Milk-based drinks and similar products intended for young children	0.15 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
		1.25 g/kg for products other than beverages
13.2	**Foods for special medical purposes as defined in Regulation (EU) No 609/2013**	
13.2	Foods for special medical purposes as defined in Regulation (EU) No 609/2013	On case-by-case basis
13.3	**Total diet replacement for weight control as defined in Regulation (EU) No 609/2013**	
13.3	Total diet replacement for weight control as defined in Regulation (EU) No 609/2013	0.5 g/L beverages
		5 g/kg products other than beverages
14	**Beverages**	
14.1.4	Flavoured drinks	0.25 g/L
17	**Food supplements as defined in Directive 2002/46/EC**	
17	Food supplements as defined in Directive 2002/46/EC	0.5 g/day for general population

3'-SL = 3'-sialyllactose sodium salt; EU = European Union; UHT = ultra-high temperature.
[a] Numbering in the reference to the Guidance document describing the food categories in Part E of Annex II to Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (version 5, updated June 2017), and the Union List Entry for 2'-FL, See Part E, Annex II Consolidated version of: http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1519051273289&uri=CELEX:02008R1333-20170818
[b] Glycom understands that this food category (typically called "growing-up milks" by industry) will be moved to another food code, and request approval under the new food code.

HMOs, including 3'-SL, do not undergo any significant digestion in the upper gastrointestinal tract; however, HMOs are orally absorbed intact to a small extent, a small portion of which (approximately 1 to 2% of the total amount of HMO ingested) is excreted unchanged in urine. Therefore, the absorption of 3'-SL would be limited and any level of the 3'-SL ingredient that is absorbed would be no different to that exposed to by infants consuming human breast milk. Therefore, the potential absorption of 3'-SL product from its consumption is not a safety concern for infants. Since infants comprise the most sensitive age group, it may be concluded that the absorption of 3'-SL does not pose a safety concern for other age groups.

Glycom's 3'-SL ingredient is neither mutagenic (as assessed in the bacterial reverse mutation test) nor clastogenic/aneugenic (as assessed in the *in vitro* mammalian cell micronucleus test). In a 90-day toxicity study conducted in neonatal Sprague Dawley rats (dosed from Day 7 of age), the no-observed-adverse-effect-level was concluded to be 5,000 mg/kg body weight/day (the highest dose test). No measurable protein residues are detected in the 3'-SL ingredient and it is inherently non-allergenic.

In addition, the safety of 6'-SL (a chemically and structurally similar isomer of 3'-SL), has also been extensively investigated in a series of preclinical and clinical studies, which further support the safety of the 3'-SL ingredient for its intended uses.

The totality of the presented data, including thorough safety assessments, highlights the safety and suitability of this ingredient for its proposed food uses.