

APPLICATION FOR THE APPROVAL OF THE HUMAN-IDENTICAL MILK OLIGOSACCHARIDE LACTO-N-FUCOPENTAOSE I (LNFP-I) AND 2'-FUCOSYLLACTOSE (2'-FL) MIXTURE (LNFP-I/2'-FL) 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

Lacto-*N*-fucopentaose I and 2'-fucosyllactose mixture (LNFP-I/2'-FL) is obtained from microbial fermentation and is isolated from a single fermentation; thus, it is not a blend of separately produced compounds. The manufactured LNFP-I and 2'-FL are identical in structure to the same molecules that are present in human milk and are therefore henceforth referred to as human-identical milk oligosaccharides (HiMOs)¹. LNFP-I and 2'-FL are two of the most abundant individual oligosaccharides of the complex natural oligosaccharide fraction of human milk.

As LNFP-I/2'-FL has not been previously added as food ingredient to infant or follow-on formula or to foods (*i.e.*, consumed to a significant degree) in the EU before 15 May 1997, it would therefore be considered a novel food under Regulation (EU) No 2015/2283² on novel foods pursuant to Art. 3, Point 2(a) and fall under the categories:

- i) Food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997; and
- ii) Food consisting of, isolated from or produced from microorganisms, fungi or algae.

Similar to previous HiMOs (*i.e.*, 2'-FL, LNnT, 2'-FL/DFL, LNT, 3'-SL, and 6'-SL) approved in the EU, LNFP-I/2'-FL is also obtained from microbial fermentation from an *E. coli* K-12 DH1-derived strain and is isolated as a highly purified simple mixture of fully characterised and related compounds. Analytical data demonstrate the absence of the production organism, its DNA, residual protein and any potential endotoxins deriving from the microorganism. The composition and specifications are well defined and fully characterise the ingredient.

LNFP-I/2'-FL is manufactured in a process that is highly contained, controlled and compliant with HACCP principles. Batch manufacturing data demonstrate that it is produced in a consistent manner and that any potential inherent process and external contaminants are below levels of safety concern. Analytical data also show LNFP-I/2'-FL is stable for its intended shelf-life, both alone and within processed food, with no evidence of hazards or harmful degradation products being formed during its storage.

It is proposed for use as ingredient in infant formulas (up to 12 months), follow-on formula, infant-specific foods and foods expressed on a basis of LNFP-I of up to 1.5 g/L and for young children at a use levels of up to 1.2 g/L or 10 g/kg in ready-to-drink and reconstituted products. LNFP-I is also intended for use in foods and beverage targeted towards older population groups (up to 1.2 g/L or 10 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 2.0 g/L or 20 g/kg), and supplements (2.0 g/day in the general population 1.0 g/day for young children and 1.2 g/day for infants). The maximum use level for formula milk is proposed on the basis of providing a similar amount of LNFP-I to that which occurs naturally in mature human breast milk.

¹ 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.

² Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001. OJ L 327, 11.12.2015, p. 1–22. Available online: <https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX:32015R2283>.

For LNFP-I and 2'-FL respectively, the highest 95th percentile exposure estimates from the full combination in all proposed foods at its maximum proposed use levels is considerably less than their highest mean consumption per day of from breast milk.

HMOs, including LNFP-I and 2'-FL, 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 LNFP-I/2'-FL would be limited and any level of LNFP-I/2'-FL product that is absorbed would no different to that exposed to by infants consuming human breast milk. Therefore, the potential absorption of LNFP-I and 2'-FL 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 LNFP-I/2'-FL does not pose a safety concern for other age groups.

The NOAEL for LNFP-I was concluded to be 5,000 mg/kg body weight/day (the highest dose tested and maximum feasible dose), based on the results of a 90-day study conducted in neonatal Sprague Dawley [CrI:CD(SD)] rats.

LNFP-I/2'-FL is neither mutagenic (as assessed in the bacterial reverse mutation test) nor clastogenic/aneugenic (as assessed in the *in vitro* mammalian cell micronucleus test). Nor does it represent any significant allergenic risk due to the absence of proteins, which are demonstrated to be removed by the production process and through assessment of the production organism using the search algorithms provided by the Allergen Online tool (ver. 20)³.

Together, the weight of the available evidence on LNFP-I/2'-FL supports the safe use of the ingredient under the proposed conditions of use.

³ FARRP (Food Allergy Research and Resource Program), 2020. AllergenOnline version 20: home of the FARRP allergen protein database. University of Nebraska-Lincoln, Food Allergy Research and Resource Program (FARRP), Lincoln, NE. Available online: <http://www.allergenonline.org/> (Released: February 10, 2020).