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To whom it may concern

FrieslandCampina Ingredients submission on Application A1155 – 2'-FL and LNnT in infant formula and other products

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Introduction

FrieslandCampina Ingredients would like to thank the Food Standards Australia New Zealand (FSANZ) for providing the opportunity to submit submissions in the 2nd call of submissions on the assessment of A1155 – 2'-FL and LNnT in infant formula and other products. We thank FSANZ for their consideration of the comments and views described in this submission.

This submission has been carefully drafted by FrieslandCampina Ingredients. FrieslandCampina Ingredients believes that every child has the right to grow up healthy. Our aim is to bring value-added, healthy and functional ingredients and solutions to the market in close cooperation with customers, especially in the areas where nutrition matters most.

FrieslandCampina Ingredients believes that breastfeeding is the preferred method of feeding an infant. If, however, breast feeding or breast milk is not available for the infant, the only suitable alternative method of feeding is an infant formula product.

FrieslandCampina Ingredients supports the FSANZ assessment that voluntary addition of 2'-FL alone or in combination with LNnT is safe and suitable for addition to infant formula products and formulated supplementary foods for young children.

Comments

FrieslandCampina Ingredients does not support the position to prohibit the addition of 2'-FL alone, or with LNnT, in combination with existing oligosaccharide permissions.

Prohibition of use with Existing Oligosaccharide Permissions

FSANZ proposes to prohibit the addition of 2'-FL alone, or with LNnT, in combination with existing permissions for GOS and inulin-type fructans (ITF) for infant formula products and formulated supplementary foods for young children (FSFYC). FSANZ states this preliminary position is based on the evidence available to assess the tolerance of infants to the total combination of oligosaccharides.

FrieslandCampina Ingredients does not support the position to prohibit the addition of 2'-FL alone, or with LNnT, in combination with existing oligosaccharide permissions. This is based on the following arguments, which are consecutively elaborated below.

1. First studies indicate that combinations with other oligosaccharides are safe
2. Other oligosaccharides have complementary effects to 2'-FL
3. Prohibition of combinations with other oligosaccharides is not consistent with other legislation

1. First studies indicate that combinations with other oligosaccharides are safe

The total level oligosaccharides in human milk is reported to be 10-15 g/L¹. This level and the composition of human milk oligosaccharides is determined by maternal genetics, lactation stage and environmental factors. In the past few decades, it has become common practice to supplement infant formula products with other types of oligosaccharides (e.g. galacto-oligosaccharides (GOS, fructo-oligosaccharides (FOS) and/or polydextrose (PDX)) at levels up to 8 g/L. Several studies have shown that addition of oligosaccharides at such levels to infant formula is well tolerated by infants and has no impact on healthy growth²⁻⁶. These findings indicate that oligosaccharide supplementation of infant formula poses no safety or tolerance risk for infants up to 8 g/L and suggest that even levels up to 15 g/L are well tolerated by infants. This supports the combination of 2'-FL alone, or with LNnT, at levels proposed in the Application with oligosaccharides previously permitted for use in infant formula. By permitting only 2'-FL at a concentration of 2.4 g/L, the total oligosaccharide level in infant formula could not approach levels found in human milk.

In addition, a number of recent clinical trials have shown combinations of 2'-FL with other oligosaccharides to be well tolerated when added to infant formula. A study in healthy infants showed that the combination of 0.2 g/L 2'-FL + 2.2 g/L GOS and a combination of 1.0 g/L 2'-FL + 1.4 g/L GOS were well tolerated and had no impact on infant growth⁷. More recently, a study showed that the combination of 0.2 g/L 2'-FL + 2.0 g/L FOS was well tolerated in healthy infants⁸; and another trial showed that addition of 0.2 g/L 2'-FL + 1.8 g/L FOS to a partially hydrolyzed formula was safe and well tolerated by extremely fussy infants⁹.

Although these studies did not use the maximum amount of oligosaccharides permitted in the Code, it would be inconsistent with the data to prohibit all combinations of 2'-FL alone (or with LNnT) with other oligosaccharides in foods for this age group.

2. Other oligosaccharides are expected to have complementary effects to 2'-FL

Next to the fact that 2'-FL has been described as a potent prebiotic¹⁰ specifically stimulating the growth of bifidobacteria^{11,12}, 2'-FL is ascribed to have the ability to inhibit binding and/or infectivity of pathogens¹³⁻¹⁵. As such, 2'-FL supplementation of infant formula may reduce the risk of infections, which has already been suggested from association studies¹⁶ as well as the first intervention studies¹⁷.

As for 2'-FL, GOS are also known for their effects on gut microbiota composition, stimulating growth of bifidobacteria and lactobacilli^{18,19}. However, on top of that, several studies have shown health benefits of GOS for infants, which have not (yet) been demonstrated for 2'-FL:

GOS is reported to improve stool consistency^{18,20}, to contribute to easy defecation^{21,22}, to stimulate the absorption of calcium²³ and iron²⁴ and to reduce the risk of allergy development (when combined with FOS)^{25,26}.

In addition to these clinical data suggesting added benefits of combining 2'-FL with e.g. GOS, recent preclinical studies have also suggested that the combination of 2'-FL with GOS:FOS can reduce rotavirus-induced diarrhea in rats with additive effects on certain mechanisms of action²⁷; and that the combination of 2'-FL with scFOS:lcFOS enhances influenza vaccine responses in mice²⁸.

So, based on the effects described for 2'-FL and other oligosaccharides (e.g. GOS, FOS), it is expected that they can have complementary effects, warranting combinations to be added to infant formula for optimal health and protection of infants.

3. Not consistent with other legislation

In our view, the proposal to prohibit the use of 2'-FL with other oligosaccharides is contrary to the requirements of FSANZ ACT Sections 3(d), 13(1)(d) and 18(2)(b) of the Food Standards Australia New Zealand Act 1991 concerning the promotion of consistency with international food standards.

The proposed prohibition of combining 2'-FL with other oligosaccharides is inconsistent with existing permissions of these novel foods. 2'-FL alone, or with LNnT, is permitted for use in infant formula products in numerous countries (e.g., European Union, United States, Singapore) without conditions related to other oligosaccharides. Developing permissions for novel foods that are inconsistent with existing permissions presents challenges to the recognized importance of harmonized food standards as globalization of the food supply continues.

Also, if Single Ingredients are approved for application in infant formula, they are generally allowed in combination (accounts for MFGM, LF, probiotics, casein, whey, etc). It is not feasible (nor ethical) to test all possible combinations of ingredients, nor do we feel that to be necessary for the combination of 2'-FL with other oligosaccharides as substantiated under point 1.

Conclusion

In the absence of public health and safety concerns and considering the evidence supporting health benefits, FrieslandCampina Ingredients:

- agrees with FSANZ's conclusion regarding public health and safety concerns associated with 2'-FL and LNnT
- supports FSANZ's proposal to permit a maximum of 2.4 g/L for 2'-FL alone, or in combination with LNnT, with no more than 0.6 g/L of LNnT
- does **NOT** support the prohibition of use with existing oligosaccharide permissions

References

1. Bode, L. The functional biology of human milk oligosaccharides. *Early Hum. Dev.* **91**, 619–622 (2015).
2. Ziegler, E. *et al.* Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *J. Pediatr. Gastroenterol. Nutr.* **44**, 359–64 (2007).
3. Veereman-Wauters, G. *et al.* Physiological and bifidogenic effects of prebiotic supplements in infant formulae. *J. Pediatr. Gastroenterol. Nutr.* **52**, 763–71 (2011).
4. Piemontese, P. *et al.* Tolerance and safety evaluation in a large cohort of healthy infants fed an

- innovative prebiotic formula: A randomized controlled trial. *PLoS One* **6**, e29010 (2011).
5. Boehm, G. *et al.* Supplementation of a bovine milk formula with an oligosaccharide mixture increases counts of faecal bifidobacteria in preterm infants. *Arch. Dis. Child. Fetal Neonatal Ed.* **86**, F178-81 (2002).
6. Closa-Monasterolo, R., Gispert-Illaurado, M., Luque, V., Ferre, N. & Rubio-torrents, C. Safety and efficacy of inulin and oligofructose supplementation in infant formula : Results from a randomized clinical trial. *Clin. Nutr.* **32**, 918–927 (2013).
7. Marriage, B. J., Buck, R. H., Goehring, K. C., Oliver, J. S. & Williams, J. A. Infants Fed a Lower Calorie Formula With 2'FL Show Growth and 2'FL Uptake Like Breast-Fed Infants. *J. Pediatr. Gastroenterol. Nutr.* **61**, 649–58 (2015).
8. Kajser, J., Oliver, J. & Marriage, B. Gastrointestinal Tolerance of Formula Supplemented with Oligosaccharides. *FASEB J* **30**, 671 (2016).
9. Reverri, E., Devitt, A., Kajzer, J., Baggs, G. & Borschel, M. Review of the Clinical Experiences of Feeding Infants Formula Containing the Human Milk Oligosaccharide 2'-Fucosyllactose. *Nutrients* **10**, 1346 (2018).
10. Yu, Z. T. *et al.* The principal fucosylated oligosaccharides of human milk exhibit prebiotic properties on cultured infant microbiota. *Glycobiology* **23**, 169–177 (2013).
11. Lewis, Z. T. *et al.* Maternal fucosyltransferase 2 status affects the gut bifidobacterial communities of breastfed infants. *Microbiome* **3**, 13 (2015).
12. Bai, Y. *et al.* Fucosylated Human Milk Oligosaccharides and N-Glycans in the Milk of Chinese Mothers Regulate the Gut Microbiome of Their Breast-Fed Infants during Different Lactation Stages. *mSystems* **3**, 1–19 (2018).
13. Weichert, S. *et al.* Bioengineered 2'-fucosyllactose and 3-fucosyllactose inhibit the adhesion of *Pseudomonas aeruginosa* and enteric pathogens to human intestinal and respiratory cell lines. *Nutr. Res.* **33**, 831–8 (2013).
14. Weichert, S. *et al.* Structural Basis for Norovirus Inhibition by Human Milk Oligosaccharides. *J. Virol.* **90**, 4843–4848 (2016).
15. Laucirica, D. R., Triantis, V., Schoemaker, R., Estes, M. K. & Ramani, S. Milk Oligosaccharides Inhibit Human Rotavirus Infectivity in MA104 Cells. *J. Nutr.* **147**, 1709–1714 (2017).
16. Morrow, A. L. *et al.* Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. *J. Pediatr.* **145**, 297–303 (2004).
17. Puccio, G. *et al.* Effects with Infant Formula with Human Milk Oligosaccharides on Growth and Morbidity: A Randomized Multicenter Trial. *JPGN* **64**, 624–631 (2017).
18. Ben, X.-M. Low level of galacto-oligosaccharide in infant formula stimulates growth of intestinal Bifidobacteria and Lactobacilli. *World J. Gastroenterol.* **14**, 6564 (2008).
19. Fanaro, S. *et al.* Galacto-oligosaccharides are bifidogenic and safe at weaning: a double-blind randomized multicenter study. *J. Pediatr. Gastroenterol. Nutr.* **48**, 82–8 (2009).
20. Williams, T. *et al.* Tolerance of infant formulas containing prebiotics in healthy, term infants. *JPGN* **59**, 653–658 (2014).
21. Costalos, C., Kapiki, a, Apostolou, M. & Papathoma, E. The effect of a prebiotic supplemented formula on growth and stool microbiology of term infants. *Early Hum. Dev.* **84**, 45–9 (2008).
22. Schmelzle, H. *et al.* Randomized Double-Blind Study of the Nutritional Efficacy and Bifidogenicity of a New Infant Formula Containing Partially Hydrolyzed Protein , a High α -Palmitic Acid Level , and Nondigestible Oligosaccharides. *JPGN* **36**, 343–351 (2003).
23. Whisner, C. M. *et al.* Galacto-oligosaccharides increase calcium absorption and gut bifidobacteria in young girls: a double-blind cross-over trial. *Br. J. Nutr.* **110**, 1292–303 (2013).
24. Paganini, D. *et al.* Consumption of galacto-oligosaccharides increases iron absorption from a micronutrient powder containing ferrous fumarate and sodium iron EDTA: a stable isotope study in Kenyan infants. *Am. J. Clin. Nutr.* **106**, 1020–1031 (2017).
25. Moro, G. *et al.* A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch. Dis. Child.* **91**, 814–819 (2006).
26. Arslanoglu, S. *et al.* Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. *J. Nutr.* **138**, 1091–1095 (2008).
27. Azagra-Boronat, I. *et al.* Supplementation with 2'-FL and scGOS/lcFOS ameliorates rotavirus-induced diarrhea in suckling rats. *J. Nutr. Biochem.* **8**, 1–17 (2018).

28. Xiao, L. *et al.* The Combination of 2 -Fucosyllactose with Long-Chain Fructo-Oligosaccharides that Enhance Influenza Vaccine Responses Is Associated with Mucosal Immune Regulation in Mice. *J Nutr* **149**, 856–869 (2019).