INFANT NUTRITION COUNCIL
AUSTRALIA & NEW ZEALAND

5 July 2023

INC SUBMISSION ON CALL FOR SUBMISSIONS – APPLICATION A1265: 2'-FL/DFL, LNT, 6'-SL SODIUM SALT AND 3'-SL SODIUM SALT AS NUTRITIVE SUBSTANCES IN INFANT FORMULA PRODUCTS

This submission has been prepared by the Infant Nutrition Council (INC). The INC represents manufacturers, marketers and suppliers of infant formula and toddler milk dinks (formulated supplementary foods for young children) and, is the key industry stakeholder in the advancement of infant nutrition representing over 95% of the volume manufactured and marketed in Australia and New Zealand.
INC aims to:

1. Improve infant nutrition by supporting the public health goals for the protection and promotion of breastfeeding and, when needed, infant formula as the only suitable alternative; and
2. Represent the infant formula product and toddler milk drink industry in Australia and New Zealand.

INC is a responsible group that voluntarily restricts its marketing practices for infant formula products to support government policies for the protection and promotion of breastfeeding.

INC believes that breastfeeding is the normal way to feed infants as it has numerous benefits for both mothers and babies. When an infant is not given breast milk the only suitable and safe alternative is a scientifically developed infant formula product. For these infants, infant formula is the sole source of nutrition for around the first 6 months. It is important that scientific advances in infant nutrition are captured and incorporated into these products to ensure the best possible outcome for infants who do not receive breast milk.

We welcome the opportunity to provide written comment to Food Standards Australia New Zealand (FSANZ) in response to the *Call for Submissions – Application A1265: 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products.*

Yours sincerely

EXECUTIVE SUMMARY

1. After lactose and fat, the third main solid component in human milk is neutral and acid oligo- (and poly) saccharides. Neutral oligosaccharides such as 2'-FL are the predominant oligosaccharides in human milk.

2. FSANZ concluded from its overall *risk and technical assessment* (safety, toxicological and microbiological assessments, dietary and nutrition assessments and beneficial health assessment) that consumption of infant formula products containing the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL alone or in combination at the levels requested was safe and well tolerated and would have a beneficial outcome.

3. INC supports the FSANZ decision to permit the addition of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL alone or in combination at the levels requested to infant formula products. INC supports the proposal to remove the current prohibition in Standard 2.9.1 on the addition to IFP of galacto-oligosaccharides (GOS) and/or inulin-type fructans (IFT) in combination with lacto-N-neotetraose (LNnT).

4. In light of existing permissions and labelling requirements, no additional labelling requirements were proposed, a position INC agrees with. INC nonetheless continues of the view that the prohibition on the use of the term, 'human identical milk oligosaccharides' or HiMO, is counter to building consumer confidence in, and understanding of, labelling information.

5. We note FSANZ is committed to reviewing new evidence on the beneficial role of a range of HiMOs in the normal growth and development of infants. INC is wholly supportive of FSANZ's ongoing work in this area.

6. Harmonisation with international standards, that are based on relevant science and scientific expert opinion, is essential to allow the manufacture and availability of these types of products for consumers in Australia and New Zealand and for export. As well, the alignment of regulations with international standards encourages consideration of future investments in innovation in Australia and New Zealand. Alignment will result after the 15 month exclusivity period.

7. INC has no comments to make on the exclusivity of this particular Application. As in previous submissions, INC is supportive of exclusive capturable commercial benefit and fully recognises the value that this has to deliver on investment for the food industry and for innovation. We continue to seek clarity and consideration around the current and future scope of the application of exclusivity in the broader food supply and its implementation.

DETAILED COMMENTS

The application

8. Glycom A/S (**Glycom**) has applied to Food Standards Australia New Zealand (**FSANZ**) to amend the Australia New Zealand Food Standards Code (**the Food Standards Code**) to permit the voluntary addition of four human-identical milk oligosaccharide (**HiMO**) products for use as nutritive substances in infant formula products. The substances and their proposed maximum permitted amounts are:
    - A mixture of 2'-fucosyllactose (**2'-FL**) and difucosyllactose (**DFL**) (**2'-FL/DFL**) (96 mg/100 kJ);
    - lacto-N-tetraose (**LNT**) (32 mg/100 kJ);
    - 6'-sialyllactose sodium salt (**6'-SL**) (16 mg/100 kJ); and
    - 3'-sialyllactose sodium salt (**3'-SL**) (8 mg/100 kJ).

9. Glycom has also requested an exclusive use permission for a period of 15 months for their combination of the above four HiMO branded substances after gazettal.

Content of human milk

10. After lactose and fat, the third main solid component in human milk is neutral and acid oligo- (and poly) saccharides. The structure of about 200 human milk oligosaccharides has been identified and many more are present, at least in small quantities. These oligosaccharides occur in concentrations between 10-15 g/L in mature breast milk and up to 20 g/L in colostrum (Kunz et al. 2000 and Thurl et al. 2017). Neutral oligosaccharides such as 2'-FL are the predominant oligosaccharides in human milk and the permitted addition in infant formula products is in line with Policy Principle (h) relating to composition in the Policy Guideline on *Regulation of Infant Formula Products*.

11. The HiMOs 2′-FL/DFL; LNT; 6′-SL and 3′-SL are all components of the human milk oligosaccharide (**HMO**) fraction of human milk. 2′-FL and DFL are oligosaccharides that contain the sugar fucose (a hexose deoxy sugar with the chemical formula $C_6H_{12}O_5$) and so are called 'fucosylated' HMOs. 2'-FL and DFL are always found together in human milk.

12. Glycom produces these oligosaccharides via a microbial fermentation process to produce the HiMOs. The fermentation is performed using a GM strain of *Escherichia coli* (***E. coli***) K-12. This method is the same as for that of the Application A1155 for the production of 2′-FL and LNnT and based on the FSANZ previous assessment as part of A1155 and the data provided by the Applicant, a biotechnology assessment of this production strain was not required.

International status

13. The European Food Safety Authority (EFSA) has issued scientific opinions on the safety of 2′-FL/DFL, LNT, 6′-SL and 3′-SL produced by the Applicant, as well as LNT, 6′-SL and 3′-SL produced by Chr. Hansen, as novel foods. Uses evaluated included addition to infant formula and follow-on formula (EFSA 2019a; EFSA 2019b; EFSA 2020b; EFSA 2020a; EFSA 2022b; EFSA 2022c; EFSA 2022a). EFSA has also published an opinion on the safety of an extension of use for Glycom's 2′-FL/DFL and LNT in food supplements for infants (EFSA 2022d). EFSA concluded that all of these substances are safe under the proposed conditions of use.

14. 2′-FL/DFL and LNT and 3'SL and 6'SL are authorised for use as novel foods in the UK under retained EU law following the exit of the UK from the EU.

15. The US Food and Drug Administration (FDA) has responded that it has 'no questions' to Glycom's self-assessments that 2′-FL/DFL, LNT, 3′-SL and 6′-SL produced by microbial fermentation are Generally Recognized as Safe (GRAS) (FDA 2020c; FDA 2020d; FDA 2020b; FDA 2020a

16. Harmonisation with international standards, that are based on relevant science and scientific expert opinion, is essential to allow the manufacture and availability of these types of products for consumers in Australia and New Zealand and for export.

Risk and Safety Assessment

17. There are already permissions to add 2′-FL and LnNT to infant formula products in the Food Standards Code.

18. FSANZ's ***toxicology assessment*** noted that 2′-FL/DFL, LNT, 6′-SL and 3′-SL produced by a microbial fermentation method of production are chemically and structurally identical to naturally occurring substances in human milk. FSANZ did not anticipate that there would be any significant differences in pharmacokinetics between naturally occurring and manufactured forms of these HMOs. Overall, the available data indicated to FSANZ that intestinal absorption was limited, and a significant proportion of HMOs reached the large intestine where they were fermented by the microbiota or excreted unchanged in the faeces. The Applicant provided FSANZ with post-marketing surveillance data that found no safety concerns following consumption of infant formula containing the mixture of 2′-FL/DFL, LNT, 6′-SL and 3′-SL, or infant formula containing 2′-FL in combination with LNnT.

19. FSANZ's ***microbiological assessment*** noted that its literature review covering the period 2017-2022 (i.e. the period after FSANZ's finalisation of Application A1155) confirmed that there were no specific microbiological adverse impacts from the addition of 2′-FL, LNT, 3′-SL and 6′-SL at the proposed concentrations to infant formula.

20. FSANZ's **dietary intake assessment** concluded that, estimated dietary intakes of HiMOs from infant/follow-on formula were similar between FSANZ and Applicant calculations. The estimated mean dietary intakes (g/kg bw/day) of 3 month olds and 9 month olds calculated by FSANZ and Glycom were very closely aligned.

21. FSANZ's ***nutritional assessment*** concluded that the amounts of 2′-FL/DFL, LNT, 6′-SL and 3′-SL requested to be added to infant formula products was within the range of human milk concentrations as reported in a recent systematic review (Soyyilmaz et al. 2021). From the three human clinical trials provided with the Application, FSANZ noted that only one used a combination of HiMOs containing the five HiMOs requested by Glycom but the accumulating body of evidence indicates that infants achieve normal growth when they are fed infant/follow-on formula containing HiMOs at the levels that are normally present in human milk. Therefore, the nutrition assessment concluded that the HiMO blend added to infant/follow-on formula did not pose a risk to the normal growth of infants.

22. FSANZ's **beneficial health effects assessment** considered anti-pathogenic and bifidogenic effects and concluded that there was no evidence that implied any antagonistic effects between the individual components. There was some evidence to support a direct effect of HiMOs on pathogenic bacteria and some viruses (e.g. norovirus and rotavirus) by fucosylated and sialylated HiMOs. The data point to the fact that the variety of human milk oligosaccharides in milk are able to collectively provide an anti-infective protection effect against a range of pathogenic microorganisms which a new-born infant is likely to be exposed to. This would support the hypothesis that a mixture of HMOs added to infant formula is likely to provide a wider range of anti-infective activity.

23. FSANZ noted there was evidence to support a role for some HiMOs, particularly 2′-FL, in inflammatory suppression and facilitating appropriate immune responses and antigenic memory. From a microbiological aspect, the development of a "healthy microbiota" is supported by the inclusion of a wider range of HiMOs to infant formula products enabling the microbiota profile to more closely resemble that of breast-fed infants.

24. FSANZ concluded from its overall ***risk and technical assessment*** that consumption of infant formula products containing a combination of four HiMOs in the Glycom application were safe and well tolerated.

Risk Management

25. On **labelling**, in light of existing permissions and labelling requirements whereby ingredients must be declared and nutrition information provided and certain representations are prohibited, no additional labelling requirements were proposed, a position INC agrees with.

26. Nonetheless, INC continues of the view that the prohibition on the use of the term, 'human identical milk oligosaccharides' or HiMO, is counter to building consumer confidence in, and understanding of, labelling information. The prohibition ignores the existing protections in the Food Standards Code and other legislation in New Zealand and Australia such as the *Fair Trading Act 1987* and the Australian Consumer Laws in the *Competition and Consumer Act 2010* concerning truthfulness of the description of ingredients by manufacturers. INC notes these terms and abbreviations are permitted to be used on labels under other internationally recognised standards.

The five-year review for 2'-FL in infant formula products

27. We note FSANZ is committed to reviewing any new evidence on the beneficial role of HiMOs in the normal growth and development of infants. INC is very supportive of this review and the gathering and analysis of relevant evidence. This Application, as with other pertinent applications, adds to this body of knowledge.

Investment in innovation

28. Alignment of regulations to permit ingredients that are safe and permitted internationally encourages consideration of future investments in innovation in Australia and New Zealand. Both countries gain consideration of future investments in innovation if regulations continue to align. Without such investment we stand to lose the public health benefits of such innovation and consign our infants to less than optimal foods in the future.

Trade impacts

29. In 15 months (after the exclusivity period), Australia and New Zealand will be aligned with other jurisdictions where these ingredients are approved both individually and in combination.

Food industry impacts

30. INC has no comments to make on the exclusivity of this particular Application. We are, however, seeking clarity and consideration around the current and future scope of the application of exclusivity in the broader food supply.

Drafting – Variation to Standard

31. INC agrees with the FSANZ draft variation to the Food Standards Code to permit the voluntary addition of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL, alone or in combination in infant formula products and that it is appropriate.

32. INC agrees with the FSANZ draft variation to the Food Standards Code to remove the prohibition on the use of ITF and/or GOS in IFP with LNnT.

References

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