INFANT NUTRITION COUNCIL
AUSTRALIA & NEW ZEALAND

17 January 2019

INC SUBMISSION ON APPLICATION A1155 – 2'-FL AND LNnT IN INFANT FORMULA AND OTHER PRODUCTS

INTRODUCTION

This submission has been prepared by the Infant Nutrition Council (INC). The INC represents the majority of companies marketing and/or manufacturing infant formula products and toddler milk drinks (formulated supplementary foods for young children) in Australia and New Zealand.

EXECUTIVE SUMMARY

INC supports safe and nutritious infant formula products and toddler milk drinks (formulated supplementary foods for young children). Application A1155 – 2'-FL and LNnT in infant formula and other products, prepared from an application from Glycom A/S, Denmark, proposes a novel food permission to add 2′-O-Fucosyllactose (2′-FL) alone or in combination with Lacto-N-neotetraose (LNnT), produced by microbial fermentation, in infant formula products and formulated supplementary foods for young children. Based on this Application for a novel food permission, Glycom A/S has applied for an exclusive permission for its brand of 2′-FL and LNnT for a period of 15 months after gazettal.

Safety and Technical Assessment

FSANZ's safety and technical assessment concluded that there were no public health and safety concerns associated with the addition of 2′-FL and LNnT in infant formula products and formulated supplementary foods for young children at the levels requested, or at higher levels consistent with levels in human milk. 2′-FL and LNnT are naturally present in human milk in a range of concentrations and ratios, providing a history of safe human exposure to these substances for breastfed infants. They are chemically and structurally identical to the naturally occurring oligosaccharides in human milk and to chemically synthesised oligosaccharides.

INC agrees with FSANZ's conclusion concerning safety aspects of 2'-FL and LNnT. Glycom A/S produces 2′-FL and LNnT by microbial fermentation using production strains Escherichia coli (E.coli) SCR6 and E.coli MP572 respectively. FSANZ found there was no safety concern but proposes that the permission be for food produced using gene technology and that this is required in accordance with Standard 1.5.2 – Food produced using gene technology and Schedule 26 (rather than novel food permission in Standard 1.5.1 and Schedule 25).
INC does NOT support FSANZ's proposed position to regulate 2'-FL and LNnT in the Food Standards Code under Standard 1.5.2 and Schedule 26 Food produced using Gene Technology and considers it is more appropriate to regulate these as novel foods.

Risk Management
The benefit of health effects considered by FSANZ in addition to safety were threefold: the anti-infective effect; bifidogenic effect; and the immune modulation, improved intestinal barrier function and alleviation of allergic responses. For infant formula products, FSANZ concluded substances that are naturally present in breast milk (such as 2′-FL and LNnT) are options for voluntary addition where the evidence supports their provision of potential beneficial health outcomes in infants. The proposed addition is consistent with the defined purpose for infant formula products in the Australia New Zealand Food Standards Code and satisfies the relevant Ministerial policy guidelines.

Used as a Nutritive Substance and Novel Foods
FSANZ's preliminary position is to permit both 2'-FL and LNnT to be *used as a nutritive substance*, and as *food produced using gene technology* derived specifically from production strains *E.coli* SCR6 (for 2'-FL) and *E.coli* MP572 (for LNnT), for use in infant formula products and formulated supplementary foods for young children.

INC supports the permission for both 2'-FL and LNnT to be voluntary additions to infant formula and formulated supplementary foods for young children. However, we note that categorising them to each be *used as a nutritive substance* is inconsistent with the approach taken in the Food Standards Code for both galacto-oligosaccharides (GOS) and inulin-type fructans. Creating such inconsistencies may create confusion and complexity to regulatory interpretation and enforcement, which could be considered within the scope of Proposals P1024 and P1028. In our view the same labelling provisions should apply to infant formula products and formulated supplementary foods for young children for all these oligosaccharide substances.

INC does NOT support FSANZ's proposed position to regulate 2'-FL and LNnT in the Food Standards Code under Standard 1.5.2 and Schedule 26 Food produced using gene technology. INC instead strongly supports alignment with treatment in the USA and the EU where they are regulated as novel foods and primacy is given to the innovation of use. This would still mean regulation within the Food Standards Code but under Standard 1.5.1 and Schedule 25 (Novel Foods).

Maximum use levels
FSANZ considered the maximum levels proposed by Glycom S/R of 2′-FL and LNnT in the context of the safety, technical and health effects assessment. It found that higher levels of 2′-FL could potentially enhance the protective effect of this substance against invasive C. jejuni infection in infants (and toddlers) and that a level of use double that requested (i.e. 2.4 g/L rather than 1.2 g/L) in infant formula and follow-on formula provides dietary intakes of 2′-FL similar to 3 and 9 month old breastfed infants. FSANZ proposes that a maximum combined total of 2.4 g/L for 2′-FL and LNnT in any ratio be permitted so long as LNnT does not exceed 0.6g/L, is safe and suitable for addition to infant formula products. FSANZ proposes that for formulated supplementary foods for young children, the maximum levels be 0.56 g/serving for 2'-FL alone or in combination with LNnT and a maximum of 0.14 g/ serving for LNnT.
INC supports the maximum levels proposed by FSANZ for 2′-FL alone, for LNnT and for their combined use in both infant formula products and formulated supplementary foods for young children.

Units of measure (mg/100kJ and g/serving)
INC considered the issues associated with studies presenting the evidence for safe and beneficial use of 2′-FL and LNnT using g/L as the Units of Measure (UoM) but the proposed permissions for Australia and New Zealand being in mg/100kJ. While INC would prefer the maximum levels to be in the UoM of the science and the international community, we can support the unit of measure proposed of mg/100kJ for infant formula products and g/serving for formulated supplementary foods for young children.

Prescribing the ingredient names
FSANZ proposes the ingredient names of '2′-fucosyllactose' and 'lacto-N-neotetraose' be prescribed without the associated acronyms although these could be added voluntarily.

INC does NOT support prescribing the ingredient names '2-fucosyllactose' and 'lacto-N-neotetraose'. Reliance for food and other substance names is generally through the application of Standard 1.2.4—4 Ingredients to be listed by common, descriptive or generic name. In our view, prescribing the names of 2'-FL and LNnT is inconsistent with the general approach throughout the Code, and certainly with similar substances such as inulin-type fructans and GOS. Such terminology is not consumer friendly.

Manufacturers would likely voluntarily label the ingredients as 2-fucosyllactose and lacto-N-neotetraose together with the associated acronyms 2'-FL and LNnT in the list of ingredients. But we raise a concern (due to space constraints and consumer reaction) in not being able to use the acronyms 2'-FL and LNnT alone in the Nutrition Information Panel. An alternative condition might be that if the full description and the acronyms are used in the ingredients list, then the acronyms alone could be used in the Nutrition Information Panel.

Specifications for 2'-FL and LNnT
FSANZ proposes that the specification includes Methods of Analysis as proposed by the applicant. INC does NOT support the inclusion of Methods of Analysis in the specification as this does not facilitate method improvement which has no impact on the safety elements of the ingredient specification.

INC supports a specification for 2'-FL and LNnT within Schedule 3 (Identity and Purity), based on what is regulated by the EU. The proposed specification does not appear to align with the most recent revision of the EU regulations.

Other comments
Labelling - Human identical milk oligosaccharides
FSANZ presents a view that the term 'human identical milk oligosaccharides' is currently prohibited due to the existing requirements in Standard 2.9.1, section 2.9.1—24. INC considers the term is not prohibited by that section and notes that use of such a technically correct description, (together with its acronym of HiMO) in addition to the technical names would be helpful for consumers.

The Application

Glycom A/S, Denmark, has applied for a novel food permission to add of 2′-*O*-Fucosyllactose (2′-FL) alone or in combination with Lacto-*N*-neotetraose (LNnT), produced by microbial fermentation, in infant formula products and formulated supplementary foods for young children..

The application, as lodged by Glycom A/S, would result in amendment to:

Schedule 25 *Permitted novel foods*, specifically the table to S25—2
Standard 2.9.1 *Infant formula products* and Schedule 29
Standard 2.9.3 *Formulated meal replacements and formulated supplementary foods*:
Division 4 *Formulated supplementary foods for young children*
Schedule 3 *Identity and purity*.

In addition, based on this Application for a novel food permission, Glycom A/S has applied for an exclusive permission for its brand of 2′-FL and LNnT for a period of 15 months after gazettal.

Safety and Technical Assessment

FSANZ's safety and technical assessment concluded that there were no public health and safety concerns associated with the addition of 2′-FL and LNnT in infant formula products and formulated supplementary foods for young children at the levels requested, or at higher levels consistent with levels in human milk.

2′-FL and LNnT are naturally present in human milk in a range of concentrations and ratios, providing a history of safe human exposure to these substances for breastfed infants. FSANZ concluded there were no public health and safety concerns associated with the addition of 2′-FL alone or in combination with LNnT to infant formula products and formulated supplementary foods for young children at the requested levels, or at higher estimated levels of dietary intakes based on 2.4 g/L 2′-FL.

This was based on 2′-FL and LNnT being chemically and structurally identical to the naturally occurring oligosaccharides in human milk and to chemically synthesised oligosaccharides, using appropriate methods of analysis (and therefore no differences in pharmacokinetics between naturally occurring and manufactured forms of 2'-FL and LNnT being expected) and the toxicological and clinical evidence not presenting concerns at the levels proposed by the applicant.

FSANZ also confirmed that intestinal absorption was limited, and a significant proportion of human milk oligosaccharides including 2'-FL and LNnT reach the large intestine where they are fermented by the microbiota or excreted unchanged in the faeces. The substances were not genotoxic in *in vitro* bacterial mutagenicity assays or in *in vitro* micronucleus assays in human lymphocytes. No adverse effects were observed in subchronic oral toxicity studies with 2'-FL or LNnT in animal studies and infant formula supplemented with 2'-FL and LNnT was well tolerated in human studies and well tolerated in a study with healthy adults.

FSANZ reviewed the effect on infant growth and concurred with the applicant that the addition of 2′-FL, alone or in combination with LNnT, to infant formula products had no effect on growth at the levels requested by the applicant.

INC agrees with FSANZ's conclusion concerning safety aspects of 2'-FL and LNnT.

Regulated as a Food Produced using Gene Technology
Glycom A/S produces 2′-FL and LNnT by microbial fermentation using production strains *Escherichia coli* (*E.coli*) SCR6 and *E.coli* MP572 respectively. FSANZ found there was no safety concern but proposes that the permission be for *food produced using gene technology* and that this is required in accordance with Standard 1.5.2 – Food produced using gene technology (rather than novel food permission in Schedule 25).

INC does NOT support FSANZ's proposed position to regulate 2'-FL and LNnT in the Food Standards Code under Standard 1.5.2 and Schedule 26 (Food produced using Gene Technology), and instead supports that they are regulated under Standard 1.5.1 and Schedule 25 (Novel Foods). We expand on this position below.

Risk Management

Health effects in terms of benefit were considered by FSANZ in addition to safety. FSANZ considered the benefits presented by Glycom A/S of anti-infective effect; bifidogenic effect; and immune modulation, improved intestinal barrier function and alleviation of allergic responses.

For infant formula products, FSANZ concluded substances that are naturally present in breast milk (such as 2′-FL and LNnT) are options for voluntary addition where the evidence supports their provision of potential beneficial health outcomes in infants. The proposed addition is consistent with the defined purpose for infant formula products in the Australia New Zealand Food Standards Code and satisfies the relevant Ministerial policy guidelines.

Used as a Nutritive Substance and Novel Foods
FSANZ's preliminary position is to permit both 2'-FL and LNnT to be *used as a nutritive substance*, and as *food produced using gene technology* derived specifically from production strains *E.coli* SCR6 (for 2'-FL) and *E.coli* MP572 (for LNnT), for use in infant formula products and formulated supplementary foods for young children.

INC supports the permission for both 2'-FL and LNnT to be voluntary additions to infant formula and formulated supplementary foods for young children. However, we note that categorising them to each be *used as a nutritive substance* is inconsistent with the approach taken in the Food Standards Code for both galacto-oligosaccharides (GOS) and inulin-type fructans which are similar substances. Creating such inconsistencies may create confusion as well as additional complexity to regulatory interpretation and enforcement, which could be considered within the scope of Proposals P1024 and P1028. In our view, the same labelling provisions should apply to infant formula products and formulated supplementary foods for young children for all these oligosaccharide substances.

While FSANZ found there was no safety concern with the production of 2'-FL and LNnT, it proposes that the permission be for *food produced using gene technology* rather than as a *novel foods*.

INC does NOT support FSANZ's proposed position to regulate 2'-FL and LNnT in the Food Standards Code under Standard 1.5.2 and Schedule 26 (Food produced using gene technology). Instead INC strongly supports alignment with treatment in the USA and the EU that primacy be given to the innovation of use and that they be regulated within the Food Standards Code under Standard 1.5.1. and Schedule 25 (Novel Foods). There is strong precedence for this.

In both the EU and USA, 2'-FL and LNnT are regulated as novel foods. Other foods listed in Schedule 26 (Foods produced using gene technology) relate to commodities such as canola and potatoes. The raw materials covered by Application A1155 are not derived from a

commodity altered using gene technology. These foods are substantially different from other foods listed in Schedule 26—3 and more aligned to foods listed in Schedule 25 which has the added benefit of listing conditions of use e.g permitted use restricted to infant formula products and formulated supplementary foods for young children.

Within the Australia and New Zealand regulatory system, 2'-FL and LNnT meet the definition of non-traditional foods and therefore should be considered novel foods. We are very concerned that all future innovation employing such technology to create substances identical to breastmilk substances (rather than the 'mimics'), would be captured under Standard 1.5.2 rather than reflective of the novel approach and innovation reflected within Standard 1.5.1. There are potential implications with trade and disincentives to innovation being made available to Australia and New Zealand consumers if regulated as currently proposed. We note that the exclusivity applied for was under the provisions of Standard 1.5.1 *Novel Foods* not Standard 1.5.2 *Foods Produced using gene technology.*

Maximum use levels

FSANZ considered the maximum levels proposed by Glycom S/R of 2′-FL and LNnT in the context of the safety, technical and health effects assessment, including estimated dietary intakes and naturally occurring levels in human milk, and other relevant matters as discussed in the following sections and at higher levels. It found that higher levels of 2′-FL could potentially enhance the protective effect of this substance against invasive *C. jejuni* infection in infants (and toddlers) and that a level of use double that requested (i.e. 2.4 g/L rather than 1.2 g/L) in infant formula and follow-on formula provides dietary intakes of 2′-FL similar to 3 and 9 month old breastfed infants. Internationally approved levels for 2′-FL range from 1.2 g/L to 2.4 g/L.

Approving a higher level of 2.4 g/L of 2′-FL alone would provide greater compatibility with a greater range of overseas food standards and allow for a more efficient and internationally competitive food industry given the high level of international interest in these substances.

In terms of the combined use of 2′-FL and LNnT, which both occur together naturally in breastmilk, there is a wide variation in the ratio of 2′-FL to LNnT present in breastmilk. FSANZ proposes that a maximum combined total of 2.4 g/L for 2′-FL and LNnT in any ratio so long as LNnT does not exceed 0.6g/L, is safe and suitable for addition to infant formula products.

A maximum level of 2.4 g/L for 2′-FL alone and for 2′-FL and LNnT combined is around three times lower than the maximum amount permitted for GOS alone or combined with inulin-type fructans (i.e. based on 8 g/L), and lower than the maximum permitted for inulin-type fructans (i.e. based on 3 g/L). FSANZ proposes that for toddler milk, the maximum levels be 0.56 g/serving for 2'-FL alone or in combination with LNnT and a maximum of 0.14 g/serving for LNnT.

INC supports the maximum levels proposed by FSANZ for 2′-FL alone, for LNnT and for their combined use in both infant formula products and formulated supplementary foods for young children.

Units of measure (mg/100kJ and g/serving)

INC considered the issues associated with the studies presenting the evidence for safe and beneficial use of 2′-FL and LNnT using g/L as the Units of Measure (UoM) but the proposed permissions for Australia and New Zealand being in mg/100kJ and g/serving. The use of g/L is the UoM for the EU, the USA and the evidential clinical papers. There is a strong case to reflect the permissions in the same UoM as used by the international community and the clinical papers (and therefore the evidence and science), noting that serve sizes can differ in the market. However, on this last point INC notes the FSANZ view that formulated

supplementary foods for young children are used as a supplement with other foods in the diet rather than as an exclusive nutritional source.

In general, INC would prefer the maximum levels to be in the UoM of the scientific and international communities, but we can support the unit of measure proposed of mg/100kJ for infant formula products and g/serving for formulated supplementary foods for young children.

Prescribing the ingredient names

FSANZ proposes to prescribe ingredient names of '2′-fucosyllactose' and 'Lacto-*N*-neotetraose', without the associated acronyms. In its view, the acronyms are unnecessary although their voluntary use in association with the relevant prescribed ingredient names would be permitted. FSANZ states that such an approach is aligned with the approach taken by the EU which requires the substances to be identified as '2′-fucosyllactose' and 'Lacto-*N*-neotetraose' on the label of the final food.

INC does NOT support prescribing the ingredient names '2'-fucosyllactose' and 'lacto-N-neotetraose'. Reliance for food and other substance names is generally through the application of Standard 1.2.4—4 *Ingredients to be listed by common, descriptive or generic name*. In our view, prescribing the names of 2'-FL and LNnT (with or without acronyms) is inconsistent with the general approach throughout the Code, and certainly with similar substances like inulin-type fructans and GOS. The prescribed names proposed are not consumer friendly and we recall the concern that very technical terminology creates for infant formula users (and the consumer reaction to create home-made bone broth for infants instead).

We note a recent study, commissioned by FSANZ and conducted in an Australian-New Zealand context (Malek *et al*, 2018) which found that

> *"…caregivers commonly experience difficulties when using labelling information, particularly when trying to identify and understand key differences between products".* Additionally, *"…mandated labelling information, particularly ingredient and nutrition information, needs to be clear and comprehensible to be effective".*

The study also found:

> *"…that explaining the scientific names/acronyms using simple 'layman's' terms would allow the information to be understood by those without a scientific background and who may be sleep-deprived".*

Manufacturers would likely voluntarily label the ingredients as 2-fucosyllactose and lacto-N-neotetraose together with the associated acronyms 2'-FL and LNnT in the list of ingredients. But we raise a concern (due to space constraints and consumer reaction) in not being able to use the acronyms 2'-FL and LNnT alone in the Nutrition Information Panel. An alternative voluntary arrangement might be that if the full description and the acronyms are used in the ingredients list, then the acronyms alone could be used in the Nutrition Information Panel.

Specifications for 2'-FL and LNnT

FSANZ proposes that the specification includes Methods of Analysis as proposed by the applicant.

INC does NOT support the inclusion of Methods of Analysis in the specification as this does not facilitate method improvement which has no impact on the safety elements of the ingredient specification.

Since the application was made and assessed by FSANZ, the EU has revised its regulations (European Commission, 2017) so that the specifications proposed by FSANZ are now out of step.

INC supports a specification for 2'-FL and LNnT within Schedule 3 (Identity and Purity), based on what is regulated by the EU. The proposed specification (as presented in sections 2.3 and 2.4 in the FSANZ SD1 for this Call for Submissions) does not appear to align to the EU.

Other comments

Labelling - Human identical milk oligosaccharides

FSANZ presents a view that the term 'human identical milk oligosaccharides' is currently prohibited due to the existing requirements in Standard 2.9.1, section 2.9.1—24. INC suggests discussion of the use of the words 'human milk identical' as it is more easily understandable by consumer.

INC does not agree that 'human identical milk' is prohibited under section 2.9.1—24 as a descriptor of ingredients. This Application is referring to two single ingredients, 2'-FL and LNnT, and 'human identical milk oligosaccharides' is not only technically correct, but is much more consumer friendly.

INC therefore does not agree with FSANZ's interpretation that section 2.9.1—24 in the Food Standards Code would prohibit the term 'human identical milk oligosaccharides' being applied. Consumers will be better informed about the nature of these ingredients if such a description, together with its acronym of HiMO, is able to be used to complement, and be used in conjunction with, their technical names.

CONCLUSION

In the absence of safety concerns, INC:

- agrees with FSANZ's conclusion concerning safety aspects of 2'-FL and LNnT
- does NOT support FSANZ's proposed position to regulate 2'-FL and LNnT in the Food Standards Code under Standard 1.5.2 and Schedule 26 (Food produced using Gene Technology) strongly supports alignment with treatment in the USA and the EU where 2'-FL and LNnT are regulated as novel foods not as GM foods
- supports the permission for both 2'-FL and LNnT to be voluntary additions to infant formula and formulated supplementary foods for young children but that categorising them to each be *used as a nutritive substance* is inconsistent with the approach taken in the Food Standards Code for both galacto-oligosaccharides (GOS) and inulin-type fructans which are similar substances.
- supports the maximum levels proposed by FSANZ for 2′-FL alone, for LNnT and for their combined use in both infant formula products and formulated supplementary foods for young children
- would prefer the maximum levels to be in the UoM of the scientific and international communities (g/L) but can support the unit of measure proposed of mg/100kJ for infant formula products and g/serving for formulated supplementary foods for young children
- does NOT support prescribing use of the ingredient names '2-fucosyllactose' and 'lacto-N-neotetraose' but rather supports application for food and other substance names through the application of Standard 1.2.4—4 *Ingredients to be listed by common, descriptive or generic name*
- considers that prescribing the full names of 2'-FL and LNnT (with or without acronyms) is inconsistent with the general approach throughout the Code.
- proposes a voluntary alternative arrangement such that if the full description and the acronyms are used in the ingredients list, then the acronyms alone could be used in the Nutrition Information Panel

- considers the term ‘human identical milk oligosaccharide’ may be used and considers that use of such a description in addition to the technical names would be helpful for consumers
- does NOT support the inclusion of Methods of Analysis in the specification as this does not facilitate method improvement
- supports a specification for 2’-FL and LNnT within Schedule 3 (Identity and Purity), based on what is regulated by the EU in its most recent regulatory revision.

REFERENCES

- European Commission (2017). Commission Implementing Regulation (EU) 2018/1023 of 23 July 2018 correcting Implementing Regulation (EU) 2017/2470 establishing the Union list of novel foods. European Commission: Brussels, Belgium.
- https://eur-lex.europa.eu/legal-content/GA/TXT/?uri=CELEX:32018R1023
- Malek L, Fowle H, Duffy G, Katzer L (2018). Informed choice or guessing game? Understanding caregivers’ perceptions and use of infant formula labelling. Public Health Nutrition, 2018, Nov 27: 1-14.