

**22 November 2018**  
**[65–18]**

## **1<sup>st</sup> Call for submissions – Application A1155**

### **2'-FL and LNnT in infant formula and other products**

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FSANZ has assessed an application made by Glycom A/S to permit the voluntary addition 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. Pursuant to section 44 of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act). FSANZ now calls for submissions to assist further consideration of the Application.

For information about making a submission, visit the FSANZ website at [information for submitters](#).

All submissions on applications and proposals will be published on our website. We will not publish material that we accept as confidential, but will record that such information is held. In-confidence submissions may be subject to release under the provisions of the *Freedom of Information Act 1991*. Submissions will be published as soon as possible after the end of the public comment period. Where large numbers of documents are involved, FSANZ will make these available on CD, rather than on the website.

Under section 114 of the FSANZ Act, some information provided to FSANZ cannot be disclosed. More information about the disclosure of confidential commercial information is available on the FSANZ website at [information for submitters](#).

Submissions should be made in writing; be marked clearly with the word 'Submission' and quote the correct project number and name. While FSANZ accepts submissions in hard copy to our offices, it is more convenient to receive submissions electronically through the FSANZ website via the link on [documents for public comment](#). You can also email your submission directly to [submissions@foodstandards.gov.au](mailto:submissions@foodstandards.gov.au).

There is no need to send a hard copy of your submission if you have submitted it by email or via the FSANZ website. FSANZ endeavours to formally acknowledge receipt of submissions within 3 business days.

### **DEADLINE FOR SUBMISSIONS: 6pm (Canberra time) 17 January 2019**

Submissions received after this date will not be considered unless an extension had been given before the closing date. Extensions will only be granted due to extraordinary circumstances during the submission period. Any agreed extension will be notified on the FSANZ website and will apply to all submitters.

Questions about making submissions or the application process can be sent to [standards.management@foodstandards.gov.au](mailto:standards.management@foodstandards.gov.au).

Hard copy submissions may be sent to one of the following addresses:

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## Supporting documents

The [following documents](#)<sup>1</sup> which informed the assessment of this Application are available on the FSANZ website:

- SD1 Safety, technical and health effects assessment
- SD2 Assessment against Ministerial Policy Guidelines

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<sup>1</sup> <http://www.foodstandards.gov.au/code/applications/Pages/A1155-2'-FL-and-LNnT-in-infant-formula-and-other-products-.aspx>

## Executive summary

Glycom A/S applied to amend the Australia New Zealand Food Standards Code (the Code) to permit the voluntary addition of 2'-O-Fucosyllactose (2'-FL), either alone or in combination with Lacto-*N*-neotetraose (LNnT), to infant formula products and formulated supplementary foods for young children (FSFYC). Permission is sought for the addition of 1.2 g/L of 2'-FL alone, or with an additional 0.6 g/L of LNnT (i.e. totalling 1.8 g/L).

FSANZ has assessed the application, but has not yet made a decision on whether to develop a food regulatory measure. FSANZ is required to seek public submissions on the findings of its assessment before making that decision. This Call for submissions provides a summary of FSANZ's assessment and states our preliminary position based on that assessment. FSANZ seeks comments on the latter in order to inform its decision on preparation of a draft variation.

2'-FL and LNnT are non-digestible oligosaccharides found naturally in human milk. The applicant's 2'-FL and LNnT are produced by microbial fermentation using genetically modified (GM) production strains. These oligosaccharides are chemically and structurally identical to those in human milk.

FSANZ's safety and technical assessment concluded that there are no public health and safety concerns associated with the addition of the applicant's 2'-FL and LNnT in infant formula products and FSFYC at the levels requested, or at higher levels consistent with levels in human milk.

The application states that 2'-FL and LNnT will provide favourable health effects of: an anti-infective effect against pathogens; bifidogenic effect; immune modulation, improved intestinal barrier function and alleviation of allergic responses.

After assessing the evidence, FSANZ concluded that the requested addition of 2'-FL alone or with LNnT has the potential to confer certain beneficial health outcomes in infants and young children (i.e. 'toddlers'). The evidence supports the plausibility of an anti-infective health effect against invasive *Campylobacter jejuni* infection and a bifidogenic effect (an increase in the relative abundance of bifidobacteria in the intestinal microflora). Other less direct evidence indicates that these accepted health effects may be enhanced as concentrations of 2'-FL (or LNnT in the case of the bifidogenic effect only) are increased. FSANZ found the evidence does not support the stated health effects associated with immune modulation, improved intestinal barrier function or alleviation of allergic responses.

Based on the evidence and the mean level of 2'-FL in mature human milk, FSANZ proposes permitting a higher maximum of 2'-FL alone than requested (i.e. from 1.2 g/L to 2.4 g/L). FSANZ notes that this higher level promotes greater consistency with 2'-FL permissions in other markets and is significantly lower than the total oligosaccharide concentration present in human milk (10–15 g/L). It is also considerably lower than the maximum for galacto-oligosaccharides (GOS) and inulin-type fructans (ITF) currently permitted in infant formula products and FSFYC (i.e. 8 g/L), which are not present in human milk or only present in trace amounts.

FSANZ proposes a maximum of 2.4 g/L for the combined use of 2'-FL and LNnT (i.e. from 1.8 g/L to 2.4 g/L). This approach differs from the applicant's request for separate maxima of 1.2 g/L 2'-FL, or 1.8 g/L 2'-FL and LNnT. However, it has the advantage of setting the same overall total for one or both requested substances. This approach was adopted for GOS and ITF.

FSANZ also proposes the requested maximum of 0.6 g/L LNnT to be permitted when used in combination with 2'-FL, noting this is within the range naturally present in human milk and is consistent with international permissions.

For consistency with existing permissions in the Code, the proposed maximum levels will be expressed in mg/100 kJ (for infant formula products) and g/serving (for FSFYC) as follows:

Infant formula products:

- If only 2'-FL added – no more than 96 mg/100 kJ of 2'-FL
- If both 2'-FL and LNnT added – no more than 24 mg/100 kJ of LNnT; and no more than 96 mg/100 kJ of 2'-FL and LNnT combined.

FSFYC:

- If only 2'-FL added – no more than 0.56 g/serving
- If both 2'-FL and LNnT added – no more than 0.14 g/serving of LNnT; and no more than 0.56 g/serving of 2'-FL and LNnT combined.

The proposed addition accords with the relevant ministerial policy guideline for infant formula products which refers to the need to demonstrate a beneficial health outcome for infants, taking into account the levels of comparable substances in human milk. In relation to the relevant ministerial policy guideline for FSFYC, the proposed addition may not strongly align with the Code's definition of the food category. However the addition is safe, provides certain potential beneficial health outcomes in toddlers, and allows alternative options to existing GOS and ITF permissions.

FSANZ's preferred approach is therefore to proceed to drafting in the 2<sup>nd</sup> Call for submissions (CFS) to permit the addition of 2'-FL alone or with LNnT to infant formula products and FSFYC. In addition to the proposed maximum levels above, FSANZ's preliminary position is to:

- Permit 2'-FL and LNnT derived specifically from the applicant's GM production strains to be *used as a nutritive substance*, and as *food produced using gene technology*.
- Prohibit the use of 2'-FL alone or with LNnT with existing permissions for GOS and ITF for infant formula products and FSFYC (i.e. permissions for 2'-FL and LNnT would be used as alternatives to GOS and ITF).
- Prescribe the ingredient names '2'-fucosyllactose' and 'Lacto-N-neotetraose' for infant formula products and FSFYC.
- Set specifications for 2'-FL and LNnT using the specifications provided by the applicant.

The proposed permission would also be subject to existing labelling requirements which help consumers to make informed purchasing decisions. Existing prohibitions for nutrition content claims and health claims and the term 'human milk-identical' (or similar terms) for infant formula products would also apply.

# 1 Introduction

## 1.1 The applicant

The application was submitted by Glycom A/S (Glycom), a Danish food ingredient manufacturer.

## 1.2 The application

The application is seeking to amend the Australia New Zealand Food Standards Code (the Code) to permit the voluntary addition of 2'-O-Fucosyllactose (2'-FL), either alone or in combination with Lacto-*N*-neotetraose (LNnT), in infant formula products<sup>2</sup> and formulated supplementary foods for young children (FSFYC)<sup>3</sup>. 2'-FL and LNnT are oligosaccharides found naturally in human milk. The application is specifically for 2'-FL and LNnT produced by microbial fermentation from genetically modified (GM) production strains *Escherichia coli* (*E.coli*) SCR6 and *E.coli* MP572 respectively. The applicant claims these oligosaccharides produced by microbial fermentation are structurally and chemically identical to 2'-FL and LNnT found in human milk.

Permission is sought for the addition of 1.2 g/L of 2'-FL alone, or with an additional 0.6 g/L of LNnT (i.e. totalling 1.8 g/L), in infant formula products and FSFYC<sup>4</sup>. The application states that these requested levels are within the ranges of 2'-FL and LNnT found naturally in mature human milk. The applicant's stated purpose is to better reflect the compositional profile of oligosaccharides of human milk. 2'-FL and LNnT produced by microbial fermentation are claimed to provide the following favourable health effects of human milk relating to microorganisms in the gastrointestinal system: anti-infective effect against pathogens; bifidogenic effect; immune modulation, improved intestinal barrier function and alleviation of allergic responses.

The application is seeking to include 2'-FL and LNnT as novel foods in the table to S25—2 of Schedule 25 (Permitted novel foods) and also notes amendments to Standard 2.9.1 (Infant formula products), Standard 2.9.3, Division 4 (Formulated supplementary foods for young children) and Schedule 3 (Identity and purity) may be required.

The applicant has also requested exclusive permission for their brand of 2'-FL and LNnT for a period of 15 months after gazettal.

## 1.3 The current standards

### 1.3.1 Australia and New Zealand

Australian and New Zealand food laws require food for sale to comply with the following Code requirements.

#### *Permitted use*

Paragraphs 1.1.1—10(5)(c) and (6)(g) of Standard 1.1.1 require that, unless expressly permitted, a food for sale must not be a food produced using gene technology, or have as an ingredient or component a food produced using gene technology.

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<sup>2</sup> 'Infant formula products' used throughout this report captures infant formula, follow-on formula and infant formula products for special dietary use.

<sup>3</sup> Toddler milk is the main type of FSFYC currently available.

<sup>4</sup> Specified in Table D.1-1 of the application dossier.

2'-FL and LNnT are both *food produced using gene technology* (section 1.1.2—2) as they are derived from an organism modified using gene technology (i.e. derived from GM production strains *E.coli* SCR6 and *E.coli* MP572 respectively). If approved, express permission for 2'-FL and LNnT derived specifically from these GM strains would be required in accordance with Standard 1.5.2 – Food produced using gene technology (rather than novel food permission in Schedule 25).

In addition, paragraph 1.1.1—10(6)(b) requires that, unless expressly permitted, a food for sale must not have as an ingredient or component a substance that was *used as a nutritive substance* (section 1.1.2—12). 2'-FL and LNnT are both also *used as a nutritive substance* because their addition to food is intended to achieve specific nutritional purposes.

#### *Infant formula products*

Standard 2.9.1 and Schedule 29 set out specific compositional and labelling requirements for the following infant formula products:

- infant formula (for infants aged 0-<12 months)
- follow-on formula (for infants aged from 6-<12 months)
- infant formula products for special dietary use (for infants aged 0-<12 months).

#### *Formulated Supplementary Food for Young Children*

Specific compositional and labelling requirements for FSFYC (for children aged 1-<4 years) are set out in Division 4 of Standard 2.9.3 and in Schedules 17 and 29.

#### *Labelling requirements*

Paragraph 1.1.1—10(8) requires that food for sale must comply with all relevant labelling requirements in the Code for that food. In addition to specific labelling requirements in Standards 2.9.1 and 2.9.3 (Division 4), the following general labelling requirements also apply.

Standard 1.2.4 generally requires food products to be labelled with a statement of ingredients.

Standard 1.2.8 generally requires food products to be labelled with nutrition information. This Standard does not apply to infant formula products (specific nutrition labelling requirements are set out in Standard 2.9.1).

Standard 1.2.7 sets out the requirements and conditions for voluntary nutrition, health and related claims made about food (FSFYC only). The Standard prohibits claims to be made about an infant formula product.

Section 1.5.2—4 sets out labelling requirements for foods for sale that consist of or have as an ingredient, food that is a *genetically modified food*. A *genetically modified food* is defined in subsection 1.5.2—4(5) as a *food produced using gene technology* that contains novel DNA or novel protein or is listed in section S26—3.

#### *Identity and purity*

Paragraph 1.1.1—15(1)(a) requires a substance that is *used as a nutritive substance* to comply with any relevant identity and purity specifications listed in Schedule 3.

### **1.3.1.1 Current oligosaccharide permissions**

The Code currently permits galacto-oligosaccharides (GOS) and inulin-type fructans (ITF) (section 1.1.2—2) to be added to infant formula products and FSFYC (sections 2.9.1—7 and 2.9.3—7). These are also permitted in general foods by their specific exclusion from the definition of ‘used as a nutritive substance’ in section 1.1.2—12 and general provisions in section 1.1.1—10. ITF includes substances such as fructo-oligosaccharides (FOS), short-chain FOS (scFOS), oligofructose and inulin (FSANZ 2013). Unlike 2'-FL and LNnT, ITF are not present in human milk and GOS is found only in trace amounts (FSANZ 2008).

For infant formula products, the Code permits the addition of ITF alone (up to 110 mg/100 kJ), GOS alone (up to 290 mg/100 kJ), or ITF and GOS combined (up to 290 mg/100 kJ, with no more than 110 mg/kJ of ITF). These amounts were converted to the respective mg/100 kJ units for Code purposes from 8 g/L of GOS (alone or combined with ITF) and 3 g/L of ITF. For FSFYC, the total amount of ITF or GOS must not be more than 1.6 g/serving (converted from 8 g/L). The permitted maximum amounts take into account both the added and naturally occurring substances.

These permissions were gazetted under [Proposal P306 – Addition of inulin/FOS & GOS to food](#) and [Application A1055 – Short-chain Fructo-oligosaccharides](#).

### **1.3.1.2 Proposal P1028 – Infant formula**

FSANZ is currently reviewing the regulation of infant formula under [Proposal P1028 – Infant Formula](#). The purpose of this proposal is to revise and clarify standards relating to infant formula and infant formula products for special dietary use comprising category definitions, composition, labelling and representation of products. No issues under review in P1028 specifically affect FSANZ’s assessment of this application.

## **1.3.2 International regulations**

2'-FL and LNnT produced by microbial fermentation (denoted as ‘micro’ in the following sections) and by chemical synthesis (denoted as ‘chem’) are permitted for use in infant formula products and FSFYC in various countries overseas.

### **1.3.2.1 Codex standards**

The current Codex Alimentarius Standards for Infant Formula and Formulas for Special Medical Purposes Intended for Infants (Codex Standard 72-1981) and for Follow-up Formula<sup>5</sup> (Codex Standard 156-1987), do not contain specific provisions for 2'-FL or LNnT. However, the standards contain provisions for ‘optional ingredients’ which would apply to the addition of substances such as 2'-FL and LNnT. FSANZ notes that the Follow-up Formula Standard is currently being reviewed by Codex<sup>6</sup>.

### **1.3.2.2 European Union**

2'-FL and LNnT are permitted as novel foods for use in a range of general foods (e.g. milk-based products, cereal bars, bread and pasta products) and special purpose foods (EU 2017a). The relevant requirements for infant formula products and milk-based drinks for young children<sup>7</sup> are:

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<sup>5</sup> ‘Follow-up Formula’ is currently defined by Codex as *a food intended for use as a liquid part of the weaning diet for the infant from the 6<sup>th</sup> month on and for young children (12-36 months)*.

<sup>6</sup> For further information, search on the [Codex Alimentarius website](#) (accessed 25 October 2018).

<sup>7</sup> ‘Infant formula’, ‘follow-on formula’, ‘foods for special medical purposes’ and ‘young children’ are defined in [Regulation \(EU\) No 609/2013](#) (accessed 17 September 2018).



- For infant formula and follow-on formula, a maximum level of 1.2 g/L of 2'-FL alone or in combination with up to 0.6 g/L of LNnT at a ratio of 2:1 in the final ready-to-use product.
- For milk-based drinks for young children, a maximum of 1.2 g/L of 2'-FL alone, or 0.6 g/L of LNnT alone or combined with up to 1.2 g/L of 2'-FL at a ratio of 1:2 in the final ready-to-use product.
- For foods for special medical purposes which includes such foods for infants, the maximum level used must be in accordance with the particular nutritional requirements of the persons for whom the products are intended.
- Prescribed specifications for:
  - 2'-FL<sub>micro</sub> and LNnT<sub>micro</sub> sourced from the GM strain *E.coli* K-12 (based on the applicant's product specifications)
  - 2'-FL<sub>micro</sub> sourced from the GM strain *E.coli* BL21 (based on another manufacturer, Jennewein Biotechnologie GmbH approval (EU 2017b)).

2'-FL<sub>micro</sub> produced using different GM strains by other manufacturers (FrieslandCampina and Dupont), have been assessed by the Medicines Evaluation Board (MEB) of Netherlands as having substantial equivalence to the existing EU permissions above (MEB 2017a, b).

### 1.3.2.3 United States

The United States Food and Drug Administration (USFDA) issued 'no questions' responses to the applicant's self-assessed Generally Recognized as Safe (GRAS) notifications for 2'-FL<sub>chem & micro</sub> for use in various general and special purpose foods (GRAS GRN 546 and 650). The maximum intended use level in 'term infant formula' and 'toddler formula' (terms used in the US) is 2.4 g/L.

The USFDA also issued 'no questions' responses to the applications for other 2'-FL<sub>micro</sub> manufacturers who use different GM production strains (Jennewein<sup>8</sup>, FrieslandCampina<sup>9</sup> and Dupont<sup>10</sup>). The maximum intended use levels for term infant formula and toddler formula is 2 g/L (Jennewein) and 2.4 g/L (FrieslandCampina and Dupont).

'No questions' responses were also issued for the applicant's LNnT<sub>chem & micro</sub> (GRAS GRN 547 and 659). The maximum intended use level of LNnT in term infant formula and toddler formula's is 0.6 g/L.

### 1.3.2.4 Singapore

The Agri-Food & Veterinary Authority has granted permission for the applicant's 2'-FL<sub>micro</sub> (up to 1.2 g/L) and LNnT<sub>micro</sub> (up to 0.6 g/L) in infant formula and follow-on formula (Singapore 2018). According to the application, their use in 'growing-up milks' (12 to 36 months) is also permitted.

### 1.3.2.5 Israel

2'-FL<sub>micro</sub> manufactured by Jennewein is authorised for use in infant formulas and follow-on formula at a maximum level of 2 g/L in the final ready-to-use product (Israel MOH 2017).

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<sup>8</sup> GRAS GRN 571

<sup>9</sup> GRAS GRN 735

<sup>10</sup> GRAS GRN 749

## 1.4 Reasons for accepting application

The application was accepted for assessment because:

- 1 it complied with the procedural requirements under subsection 22(2)
- 2 it warranted the variation of a food regulatory measure.

## 1.5 Procedure for assessment

The application is being assessed under the Major procedure<sup>11</sup> (which means it includes two rounds of public consultation). Stakeholder submissions to this assessment summary will inform a decision on preparation of a draft variation to the Code.

FSANZ extended the consideration period for the application by 6 months under subsection 109(4) of the *Food Standards Australia New Zealand Act 1991*. We determined that it was not practicable to consider the application within the 12 month consideration period (for a Major procedure) due to its complexity.

# 2 Summary of the assessment

## 2.1 Safety, technical and health effects assessment

The safety, technical and health effects assessment (see SD1) comprised:

- (i) a food technology assessment of 2'-FL and LNnT
- (ii) a safety assessment to identify potential adverse effects associated with 2'-FL and LNnT
- (iii) a dietary intake assessment to estimate the total dietary intake of 2'-FL and LNnT for breastfed infants and the intake resulting from the addition of 2'-FL and LNnT to infant formula products and FSFYC
- (iv) an assessment of the health effects claimed by the applicant.

### 2.1.1 Safety and technical assessment

The food technology assessment concluded that the applicant's 2'-FL and LNnT are chemically and structurally identical to the naturally occurring oligosaccharides in human milk and to chemically synthesised oligosaccharides, using appropriate methods of analysis. The shelf-life and specifications are appropriate for addition to infant formula products and FSFYC.

The GM safety assessment concluded that no public health and safety concerns are identified for 2'-FL and LNnT derived from genetically modified *E. coli* K-12, production strains SCR6 and MP572, respectively.

Based on an assessment of the available toxicological and clinical evidence for 2'-FL and LNnT, it was concluded that 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 FSFYC, at the levels requested by the applicant and at the estimated levels of dietary intake based on 2.4 g/L of 2'-FL and 0.6 g/L of LNnT. Since the applicant's 2'-FL and LNnT are structurally and chemically identical to the forms of these substances present in human milk, no differences in pharmacokinetics between naturally occurring and manufactured forms of 2'-FL and LNnT are expected. Overall, the available data indicated that intestinal absorption

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<sup>11</sup> The Major procedure is used when the variation of the food regulatory measure being considered involves a significant change to the scope of the measure and is of significant technical and scientific complexity.

is limited, and a significant proportion of human milk oligosaccharides (HMOs) including 2'-FL and LNnT reach the large intestine where they are fermented by the microbiota or excreted unchanged in the faeces.

Both 2'-FL and LNnT produced by microbial fermentation 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 juvenile rats at doses up to 5000 mg/kg bw/day. In human studies, infant formula supplemented with 2'-FL and LNnT was well tolerated with age-appropriate increases in body weight and other growth measures, and no significant increases in adverse events. 2'-FL and LNnT were also well tolerated in a study with healthy adults.

The assessment of effect on infant growth concluded that the addition of 2'-FL, alone or in combination with LNnT, to infant formula products has no effect on growth at the levels requested by the applicant. Also, based on a lack of adverse effects on growth in the clinical studies reviewed and the limited gastrointestinal absorption of 2'-FL and LNnT, there is no evidence to indicate a nutritional concern at the concentrations of these oligosaccharides that are typically observed in human milk.

The concentration of 2'-FL in infant formula / follow-on formula / FSFYC considered in the dietary intake assessment was 2.4 g/L (rather than 1.2 g/L as requested) as this level is similar to the mean concentration in mature human milk (2.4–3.0 g/L for 2'-FL secretors, which represents approximately 80% of women worldwide). This is about one fifth of the total concentration of oligosaccharides present in mature human milk (10–15 g/L). The estimated dietary intake of 2'-FL based on 2.4 g/L is similar to 2'-FL intakes for 3 and 9 month old breastfed infants. Estimated mean intakes of 2'-FL from FSFYC based on 2.4 g/L for 12 month old infants and 2-3 year old children, are similar to or less than those for younger formula-fed and breast-fed infants (<12 months).

The applicant's requested maximum of 0.6 g/L LNnT in infant formula products and FSFYC was considered in the dietary intake assessment. The mean concentration of LNnT in mature human milk is 0.28–0.31 g/L, noting all human milk contains LNnT. The estimated dietary intake of LNnT is therefore higher than that for 3 month and 9 month old breastfed infants due to the requested concentration being higher than the mean concentration in human milk. However, the use level of 0.6 g/L is within the range of LNnT concentrations in mature human milk (0.09–1.08 g/L). Estimated mean intakes of LNnT from FSFYC for 12 month old infants and 2–3 year old children are similar to or lower than those for younger formula-fed infants (<12 months).

Overall, 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 concludes there are no public health and safety concerns associated with the addition of 2'-FL alone or in combination with LNnT to infant formula products and FSFYC at the requested levels, or at higher estimated levels of dietary intakes based on 2.4 g/L 2'-FL.

### **2.1.2 Health effects assessment**

The assessment of anti-pathogenic effect concluded that the addition of 2'-FL to infant formula products and FSFYC may be protective against invasive *Campylobacter jejuni* (*C. jejuni*) infection through binding inhibition. The plausibility of this health effect is supported by evidence from a human study showing decreased incidence of *Campylobacter* associated diarrhoea in infants of mothers with a higher proportion of 2'-FL in their human milk, an *in vivo* murine model demonstrating decreased disease severity in animals fed 5 g/L 2'-FL, cell and antigen binding studies demonstrating a specific interaction between invasive *C. jejuni* strains and 2'-FL and *in vitro* binding inhibition studies. Based on the evidence assessed, FSANZ considers that this protective health effect could occur at the level of 2'-FL requested,

although the extent of the effect in infants and young children at this level cannot be determined. The evidence for a health effect of 2'-FL and LNnT protecting against other pathogens and toxins is inconclusive and is primarily limited to *in vitro* inhibition studies. A single human infant trial study provided limited evidence of a decreased rate of bronchitis and lower respiratory tract infection in infants fed formula supplemented with 2'-FL and LNnT. However, the reproducibility of this finding in multiple populations has not been demonstrated and is therefore inconclusive.

The assessment of bifidogenic effect concluded that the ability of *Bifidobacterium* spp. to metabolise 2'-FL and LNnT is variable within and between species and that a bifidogenic effect is plausible if the *Bifidobacterium* strains present in the infant and toddler colon are able to metabolise 2'-FL or LNnT. A single study, published as abstracts, demonstrated that infants fed formula supplemented with 2'-FL and LNnT at levels similar to those requested, had a gut microbiome at 3 months of age that more closely resembled that of breastfed infants and with a higher relative abundance of *Bifidobacterium* spp. compared to infants fed unsupplemented formula. As the reproducibility of this study has not been demonstrated in other populations the results are inconclusive. However, the plausibility of a bifidogenic effect occurring due to the requested addition of 2'-FL alone or with LNnT is further supported by a single clinical feeding trial for adults that showed a shift in the gut microflora to a higher relative abundance of bifidobacteria in a dose dependent manner following supplementation with either 2'-FL or LNnT alone or in combination at a 2:1 ratio of 2'-FL:LNnT.

The assessment of immune modulation and improved barrier function concluded that there is insufficient evidence to support the assertion that infant formula supplemented with 2'-FL alone or with LNnT will have an immune modulating effect or improve barrier function in infants and toddlers. The evidence to support these proposed health effects are largely based on *in vitro* studies and are not well supported by *in vivo* animal models or infant feeding studies. Of clinical significance in the assessment of food allergies, the available evidence demonstrates that 2'-FL does not prevent the production of allergen-specific IgE-immunoglobulins after sensitisation has occurred, and therefore 2'-FL does not protect against anaphylaxis.

Overall, the evidence assessed by FSANZ supports the plausibility of an anti-infective health effect against invasive *C. jejuni* infection and a bifidogenic effect; but does not support the health effects associated with immune modulation, improved intestinal barrier function or alleviation of allergic responses. Evidence from an *in vitro* laboratory study for anti-infective effect and an adult study for bifidogenic effect, indicates that these health effects may be enhanced as concentrations of 2'-FL (or LNnT in the case of the bifidogenic effect only) are increased.

## 2.2 Risk management

Breastfeeding is the recommended way to feed infants. However, a safe and nutritious substitute for human milk is needed for infants who are not breastfed. As infants and young children (i.e. 'toddlers') are vulnerable population groups, infant formula products and FSFYC are regulated by prescriptive provisions for the composition and labelling of these products. Any changes to the composition of these products must be established as safe prior to being permitted.

Since the safety, technical and health effects assessment (SD1) concluded that there are no public health and safety concerns associated with the addition of 2'-FL alone or with LNnT in a wide range of ratios and at levels up to 2.4 g/L to infant formula products and FSFYC, FSANZ also had regard to the matters covered in the following two Ministerial Policy Guidelines (see SD2):

- Regulation of infant formula products<sup>12</sup>
- Intent of Part 2.9 – Special purpose foods of the Code<sup>13</sup>

The infant formula policy guideline refers to the need to demonstrate a beneficial health effect or outcome for formula-fed infants, taking into account the levels of comparable substances in human milk. The intent of Part 2.9 policy guideline refers to the need for the proposed change to be consistent with the intended purpose of the food.

## 2.2.1 Health effects

FSANZ has assessed each of the favourable health effects of 2'-FL and LNnT stated in the application: anti-infective effect; bifidogenic effect; and immune modulation, improved intestinal barrier function and alleviation of allergic responses.

### 2.2.1.1 Anti-infective effect

The current available evidence for 2'-FL supports a potential protective inhibitory effect against invasive *Campylobacter jejuni* (*C. jejuni*) infection in infants and toddlers. Human and animal studies provided evidence which linked this protective effect to a potential beneficial health outcome of decreased incidence of invasive *Campylobacter* associated diarrhoea. *In vitro* binding studies and inhibition assays showed a specific interaction between invasive *C. jejuni* strains and 2'-FL. As discussed in section 2.1.2, FSANZ considers that this potential protective health effect could occur at the requested level of 2'-FL, although the extent of the effect cannot be determined. As observed in an *in vitro* study, it is possible that higher concentrations of 2'-FL could enhance the anti-infective effect. No studies were provided which demonstrated a protective effect of LNnT against invasive *C. jejuni* infection.

As discussed in section 2.1.2, the current available evidence for the stated protective effects of 2'-FL or LNnT against other pathogens and toxins identified in the application, or for decreased rates of bronchitis or respiratory tract infection in infants, is inconclusive. These stated health effects are therefore not supported by the evidence.

### 2.2.1.2 Bifidogenic effect

For the purposes of this assessment, as discussed in the SD1 report, we have defined bifidogenic effect as the proliferation and increase in the relative abundance of bifidobacteria in the intestinal microflora. FSANZ has previously recognised (under Proposal P306 and Application A1055) that the dominance of *Bifidobacterium* in the intestinal microflora is generally considered to be beneficial to the host.

The current available evidence supports the plausibility of a bifidogenic effect at the requested levels of addition of 2'-FL alone or with LNnT, providing the *Bifidobacterium* which metabolise these oligosaccharides are present in the infant or toddler gut. The plausibility of a bifidogenic effect occurring in infants and toddlers is based on the combination of evidence from *in vitro* studies and human studies in infants and adults (noting that evidence suggests that the gut microflora of toddlers is progressively more similar to that of adults than infants). FSANZ notes that the adult study showed a dose dependent relationship for a bifidogenic effect, in which higher levels of 2'-FL and/or LNnT were associated with a higher relative abundance of bifidobacteria.

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<sup>12</sup> [Policy guideline on infant formula products](#) (accessed 25 September 2018)

<sup>13</sup> [Policy guideline on intent of Part 2.9](#) (accessed 25 September 2018).

### **2.2.1.3 Immune modulation, intestinal barrier function and allergic response**

As discussed in section 2.1.2, the current available evidence for the stated immune modulating effect, improved intestinal barrier function, and protective effects against allergic responses for 2'-FL and LNnT is insufficient. These stated health effects are therefore not supported by the evidence.

### **2.2.1.4 Health effects conclusion**

#### *Infant formula products*

FSANZ concludes that the requested addition of 2'-FL alone or combined with LNnT to infant formula products is safe and supported by appropriate evidence in providing certain potential beneficial health outcomes in infants, noting that the identified beneficial health effects may be enhanced as concentrations of 2'-FL (or LNnT in the case of the bifidogenic effect only) are increased. In reaching this conclusion, FSANZ notes that 2'-FL and LNnT occur naturally in human milk; and approval of these substances would provide alternative options to existing non-digestible oligosaccharides permitted for voluntary use in infant formula products, which are not present in human milk (ITF) or only present in trace amounts (GOS). The requested addition is also consistent with the Code's defined purpose for infant formula products and accords with the relevant Ministerial policy guidelines (see SD2).

FSANZ's preliminary position is to therefore permit the addition of 2'-FL alone or combined with LNnT to infant formula products. Consideration of the proposed levels of use in infant formula products is discussed in Section 2.2.3.1 below.

#### *FSFYC*

FSANZ concludes that the requested addition of 2'-FL alone or combined with LNnT in FSFYC is safe and supported by appropriate evidence in providing certain potential beneficial health outcomes in toddlers, noting that the identified health effects may be enhanced as concentrations of 2'-FL (or LNnT in the case of the bifidogenic effect only) are increased. Although the addition of these substances may not have strong alignment with the Code's definition of FSFYC, the addition is safe, may provide beneficial health outcomes in toddlers, and provides alternative options to existing non-digestible oligosaccharides (GOS and ITF) permitted for use in FSFYC.

FSANZ's preliminary position is to therefore permit the addition of 2'-FL alone or combined with LNnT to FSFYC. Consideration of the proposed levels of use in FSFYC is discussed in Section 2.2.3.2 below.

## **2.2.2 Permitted use**

In permitting 2'-FL and LNnT as proposed above, express permission would be provided for both 2'-FL and LNnT to be *used as a nutritive substance* and as *food produced using gene technology* (as discussed in section 1.3.1); noting that no public health and safety concerns have been identified for these substances derived from the applicant's GM production strains. The applicable GM labelling requirements are discussed in section 2.2.5.4 below.

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 GM production strains *E.coli* SCR6 (for 2'-FL) and *E.coli* MP572 (for LNnT), for use in infant formula products and FSFYC.

### 2.2.3 Maximum use levels and units expression

FSANZ has considered the maximum requested levels 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.

#### 2.2.3.1 Infant formula products

As the safety, technical and health effects assessment concluded that there are no public health and safety concerns associated with the addition of 2'-FL alone or with LNnT to infant formula products at the requested levels, or at higher estimated levels of dietary intakes based on 2.4 g/L 2'-FL, FSANZ has also considered the levels of use in relation to potential beneficial health outcomes, international regulations and existing permissions for other non-digestible oligosaccharides.

As discussed in section 2.2.1.1, higher levels of 2'-FL could potentially enhance the protective effect of this substance against invasive *C. jejuni* infection in infants (and toddlers). As noted in section 2.1.1, 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, the permitted levels of 2'-FL for use in infant formula and follow-on formula range from 1.2 g/L to 2.4 g/L. Approving a higher level of 2.4 g/L of 2'-FL alone for use in Australia and New Zealand would therefore 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.

Regarding the combined use of 2'-FL and LNnT, as discussed in SD1, where 2'-FL and LNnT occur together naturally in human milk (in the majority of women) there is shown to be a wide variation in the ratio of 2'-FL to LNnT present from about 1:1 to greater than 10:1. FSANZ therefore considers that a maximum combined total of 2.4 g/L for 2'-FL and LNnT in any ratio, is safe and suitable for addition to infant formula products. This proposed combined total is 33% higher than the amount requested (i.e. from 1.8 g/L to 2.4 g/L). This approach differs from the applicant's request for separate maxima of 1.2 g/L 2'-FL or 1.8 g/L combined but has the advantage of setting the same overall total for one or both requested substances. This same approach was adopted for GOS and ITF. When used in combination, the requested maximum of 0.6 g/L LNnT is proposed to be permitted, noting this is within the range naturally present in mature human milk and is consistent with international permissions.

As discussed in section 2.2.1.4, approval of 2'-FL and LNnT would provide alternative options to existing oligosaccharides permitted for use in infant formula products. In comparison to these existing permissions, FSANZ notes that a maximum 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 ITF (i.e. based on 8 g/L), and lower than the maximum permitted for ITF (i.e. based on 3 g/L). We also note that a maximum of 2.4 g/L is significantly lower than the total concentration of oligosaccharides present in mature human milk (i.e. 10–15 g/L).

FSANZ is also proposing to prohibit the use of existing GOS and ITF permissions in combination with 2'-FL and LNnT, as further discussed in section 2.2.4. As such, there would be no cumulative increase to the total oligosaccharide load consumed by infants.

Based on the available evidence, including comparative levels in human milk and other relevant matters considered above, FSANZ proposes to permit a maximum of 2.4 g/L of 2'-

FL alone in infant formula products; and a total maximum of 2.4 g/L for 2'-FL and LNnT combined, with no more than 0.6 g/L of LNnT. For consistency with existing permissions for the addition of substances to infant formula products in the Code, FSANZ proposes to convert the maximum levels to mg/100 kJ units as set out below (further discussion about this approach is provided in Attachment A).

These maximum permitted amounts would capture both naturally-occurring and added 2'-FL and LNnT. Noting that the concentration of naturally occurring 2'-FL and LNnT in cow's or goat's milk is low or not present (see SD1), the amounts present in infant formula products and FSFYC would primarily be based on added 2'-FL and LNnT.

FSANZ's preliminary position is to permit the following maximum levels for addition to infant formula products:

- If only 2'-FL added – no more than 96 mg/100 kJ of 2'-FL
- If both 2'-FL and LNnT added – no more than 24 mg/100 kJ of LNnT; and no more than 96 mg/100 kJ of 2'-FL and LNnT combined.

### **2.2.3.2 FSFYC**

To provide a consistent regulatory approach across infant formula products and FSFYC, FSANZ also considered a maximum permitted level of 2.4 g/L of 2'-FL alone in FSFYC; and a total maximum of 2.4 g/L of 2'-FL and LNnT combined, with no more than 0.6 g/L of LNnT.

As discussed in section 2.1.1, there are no public health and safety concerns for FSFYC at the estimated levels of dietary intake based on 2.4 g/L of 2'-FL or 0.6 g/L of LNnT. Although not directly comparable, FSANZ notes that these estimated intakes for 2'-FL or LNnT from FSFYC in toddlers are less than the intakes for the more vulnerable 3 month old infants who are exclusively formula-fed, and for whom intakes based on 2.4 g/L of 2'-FL or 0.6 g/L of LNnT are safe.

As discussed for infant formula products above, higher levels of 2'-FL could potentially enhance the protective effect of 2'-FL against invasive *C. jejuni* infection in toddlers. There is also some evidence that higher levels of 2'-FL and/or LNnT could increase the abundance of bifidobacteria in the gut microflora as discussed in section 2.2.1.2.

Also similar to the infant formula products discussion, a maximum permitted level of 2.4 g/L of 2'-FL (rather than 1.2 g/L) would promote greater compatibility with international permissions for FSFYC. A maximum of 2.4 g/L for 2'-FL alone and for 2'-FL and LNnT combined, is also lower than the total level currently permitted for GOS or ITF in FSFYC (i.e. based on 8 g/L); and a maximum of 0.6 g/L of LNnT is consistent with international FSFYC permissions.

FSANZ therefore proposes to permit a maximum of 2.4 g/L for 2'-FL alone in FSFYC; and a total maximum of 2.4 g/L for 2'-FL and LNnT combined, with no more than 0.6 g/L of LNnT. For consistency with existing permissions for the addition of substances to FSFYC in the Code, FSANZ proposes converting these maximum permitted amounts to g/serving units as set out below (further discussion about this approach is provided in attachment A). These maximum amounts would capture both naturally-occurring and added 2'-FL and LNnT.



FSANZ's preliminary position is to permit the following maximum levels for addition to FSFYC:

- If only 2'-FL added – no more than 0.56 g/serving
- If both 2'-FL and LNnT added – no more than 0.14 g/serving of LNnT; and no more than 0.56 g/serving of 2'-FL and LNnT combined.

#### **2.2.4 Prohibition of use with existing oligosaccharide permissions**

FSANZ notes that the applicant is not seeking use of the proposed permissions for 2'-FL and LNnT together with existing permissions for GOS and ITF in infant formula products or FSFYC. We have, however, considered the available evidence for this potential combined use. As discussed in SD1, no adverse effects were reported in infant studies which tested formula supplemented with 2'-FL in combination with scFOS or GOS. However, the maximum amounts of scFOS or GOS permitted in the Code were not tested in these studies. Additionally, no evidence was provided which investigated the use of 2'-FL combined with both GOS and scFOS (i.e. GOS and scFOS are currently permitted to be used in combination in infant formula products in the Code). As such, the tolerance of infants to this total combination of added oligosaccharides could not be determined, noting also that this combination does not occur naturally in human milk.

Based on the available evidence, and given the combined use of the proposed and existing permissions is not requested, FSANZ proposes prohibiting the use of 2'-FL and LNnT in combination with existing GOS and ITF permissions.

FSANZ's preliminary position is to prohibit the addition of 2'-FL alone, or with LNnT, in combination with existing permissions for GOS and ITF for infant formula products and FSFYC (i.e. permissions for 2'-FL and LNnT would be used as alternatives to GOS and ITF).

#### **2.2.5 Labelling**

##### **2.2.5.1 Statement of ingredients**

Standard 1.2.4 – Information requirements – statement of ingredients requires food for sale to be labelled with a statement of ingredients unless exempt. The label on a package of infant formula products and FSFYC must contain a statement of ingredients. Should manufacturers choose to add 2'-FL alone or combined with LNnT to these foods, then these substances will be required to be declared in the statement of ingredients.

Generic ingredient labelling provisions in section 1.2.4—4 require ingredients to be identified using a name by which they are commonly known, or a name that describes its true nature, or a generic ingredient name if one is specified in Schedule 10 – Generic names of ingredients and conditions for their use.

In addition to generic ingredient labelling provisions, FSANZ has considered 2'-FL and LNnT as ingredients in the context of section 2.9.1—24 - Prohibited representations in Standard 2.9.1. This section states that *the word 'humanised' or 'maternalised' or any word or words having the same or similar effect and information relating to the nutritional content of human milk* are prohibited on infant formula product labels. Section 2.9.1—24 is underpinned by the Ministerial Policy Guideline on the Regulation of Infant Formula Products.

The term 'human milk-identical' or similar terms would be prohibited for use on infant formula products in accordance with the existing requirements in section 2.9.1—24. Currently, there

is no similar labelling prohibition for FSFYC. FSANZ is of the view that if 2'-FL and LNnT are identified on FSFYC using terminology such as 'human milk-identical', consumers may perceive infant formula products containing the same substances to be equivalent to human milk. This would contradict policy principle I of the Ministerial Policy Guideline (see SD2). FSANZ therefore considers it appropriate to prescribe the ingredient names for declaration on infant formula products and FSFYC to achieve a consistent and uniform disclosure of these ingredients.

The applicant has referred to other countries where infant formula containing 2'-FL and LNnT is sold using the ingredient declaration "2'-O-Fucosyllactose (2'-FL)" and "Lacto-N-neotetraose (LNnT)", and suggested these ingredient names will be used in Australia and New Zealand for infant formula products and FSFYC.

FSANZ proposes to require the ingredient names "2'-fucosyllactose" and "Lacto-*N*-neotetraose", without the associated acronyms. In our view, the acronyms are unnecessary although their voluntary use in association with the relevant prescribed ingredient names would be permitted. Further, this regulatory approach aligns 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<sup>14</sup>.

FSANZ's preliminary position is to prescribe the ingredient names '2'-fucosyllactose' and 'Lacto-*N*-neotetraose' for infant formula products and FSFYC.

### **2.2.5.2 Mandatory nutrition information**

For infant formula products, section 2.9.1—21 regulates the declaration of nutrition information in a nutrition information statement on the label. The nutrition information statement is a single statement and may be in the form of a table, as indicated in section S29—10 - Guidelines for infant formula products.

Paragraph 2.9.1—21(1)(iii) requires the average amount of each vitamin and mineral and any other substance *used as a nutritive substance* permitted by the standard to be declared in the nutrition information statement. As FSANZ proposes to permit both 2'-FL and LNnT to be *used as a nutritive substance* in infant formula products, when they are used, they must be declared in the nutrition information statement.

For FSFYC, the existing general requirements in Standard 1.2.8 – Nutrition information requirements would apply. That is, the addition of 2'-FL alone or with LNnT to FSFYC as ingredients, would not trigger a mandatory declaration in the nutrition information panel (NIP) unless a claim requiring nutrition information (a nutrition content claim or a health claim) is made.

When a nutrition content claim is made, the property of the food that is the subject of the claim dictates how the declaration should be made in the NIP. For example, if a nutrition content claim about dietary fibre is made for 2'-FL or LNnT, the NIP must include a declaration of the presence of dietary fibre in accordance with section 1.2.8—6(5).

### **2.2.5.3 Voluntary representations**

Subsection 1.2.7—4(b) of Standard 1.2.7 states that a nutrition content claim or health claim must not be made about an infant formula product.

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<sup>14</sup> [Commission Implementing Regulation \(EU\) 2017/2470](#) (accessed 17 September 2018).

The prohibition is also set out in section 2.9.1—24 (1)(f) of Standard 2.9.1, which prohibits a reference to the presence of a nutrient or substance that may be used as a nutritive substance, except for a statement relating to lactose, a statement of ingredients or a declaration of nutrition information.

This regulatory approach is consistent with the Policy Guideline on Nutrition, Health and Related Claims<sup>15</sup> and the Policy Guideline on the Regulation of Infant Formula Products (specific policy principle n, see SD2).

The existing prohibition for nutrition content claims and health claims for infant formula products would apply to 2'-FL and LNnT. As set out in paragraph 2.9.1—24(1)(f) of the Code, these substances would not be captured as nutrition content claims by virtue of their declaration being mandatory in the nutrition information statement.

In contrast, there is no prohibition in the Code for nutrition content claims or health claims to be made about FSFYC. Existing claim requirements and conditions set out in Standard 1.2.7 and Schedule 4 – Nutrition, health and related claims would therefore apply to FSFYC.

#### **2.2.5.4 Labelling as 'genetically modified'**

As discussed in the safety, technical and health effects assessment (SD1), 2'-FL and LNnT are highly unlikely to contain novel protein or DNA due to the purification step used in the production of these oligosaccharides.

It is therefore highly unlikely that novel protein will be present in an infant formula product or FSFYC that contains 2'-FL or LNnT as ingredients. However, where novel protein is present, the requirement to label 2'-FL or LNnT as 'genetically modified' would apply in accordance with section 1.5.2—4 of Standard 1.5.2.

#### **2.2.6 Specifications for 2'-FL and LNnT**

Since no specifications currently exist for 2'-FL or LNnT in Schedule 3, FSANZ proposes inserting the specifications provided in the application into the Code. As discussed in SD1, these specifications are approved for use in the EU and US, and relate to the applicant's 2'-FL and LNnT produced by microbial fermentation.

FSANZ's preliminary position is to set specifications for 2'-FL and LNnT using those provided by the applicant.

#### **2.2.7 Exclusivity**

An applicant may request exclusive permission for a period of 15 months to recognise the investment made in developing the food or ingredient or nutritive substance and the need to achieve return on this investment, thereby supporting innovation. Following the 15 month period, the permission would revert to a general approval for the class of food.

An exclusivity permission in the Code does not, and cannot, prevent approval of second or subsequent applications either within the exclusive use period or during the progression of an application, for the use of the same food or ingredient by other food companies, providing the application process is undertaken.

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<sup>15</sup> [Policy guideline on Nutrition, Health and Related Claims](#) (accessed 25 September 2018)

The applicant has requested exclusivity for their specific brand of 2'-FL and LNnT<sup>16</sup> on the basis that they, and their business partners, have invested significantly in the technology development and safety studies. FSANZ notes, however, that approval of both 2'-FL and LNnT as food produced using gene technology derived specifically from the applicant's GM production strains, and the proposed specifications discussed above, may provide exclusive permission to the applicant without the need for a specific brand name. FSANZ will further consider this matter in the 2<sup>nd</sup> Call for Submissions (CFS) when developing the specific drafting.

### 2.2.8 Risk management conclusion

Following consideration of the objectives of the FSANZ Act (see section 2.4) and relevant Ministerial Policy Guidelines (see SD2), FSANZ's preferred approach is to proceed to drafting in the 2<sup>nd</sup> CFS to permit the voluntary addition of 2'-FL alone, and 2'-FL and LNnT combined, to infant formula products and FSFYC.

FSANZ's proposed regulatory measures in permitting 2'-FL and LNnT in the Code are summarised in the following list.

#### **Summary of FSANZ's preliminary position on regulatory measures**

- Permit both 2'-FL and LNnT to be *used as a nutritive substance*, and as *food produced using gene technology* derived specifically from the GM production strains *E.coli* SCR6 (for 2'-FL) and *E.coli* MP572 (for LNnT), for use in infant formula products and FSFYC.
- Set a maximum permitted use level of 2.4 g/L for 2'-FL alone; and a total maximum level of 2.4 g/L for 2'-FL and LNnT combined with no more than 0.6 g/L of LNnT. For consistency with existing voluntary permissions for infant formula products and FSFYC, these levels will be expressed in mg/100 kJ and g/serving as follows:
  - Infant formula products:
    - If only 2'-FL added – no more than 96 mg/100 kJ of 2'-FL
    - If both 2'-FL and LNnT added – no more than 24 mg/100 kJ of LNnT; and no more than 96 mg/100 kJ of 2'-FL and LNnT combined.
  - FSFYC:
    - If only 2'-FL added – no more than 0.56 g/serving
    - If both 2'-FL and LNnT added – no more than 0.14 g/serving of LNnT; and no more than 0.56 g/serving of 2'-FL and LNnT combined.
- Prohibit the use of 2'-FL alone or with LNnT in combination with existing permissions for GOS and ITF for infant formula products and FSFYC (i.e. permissions for 2'-FL and LNnT would be used as alternatives to GOS and ITF).
- Prescribe the ingredient names '2'-fucosyllactose' and 'Lacto-N-neotetraose' for infant formula products and FSFYC.
- Set specifications for 2'-FL and LNnT using the specifications provided by the applicant.

The specific drafting for these proposed measures will be detailed in the 2<sup>nd</sup> CFS if FSANZ decides to prepare a draft variation after considering submissions received in response to this 1<sup>st</sup> CFS. Any such drafting will not extend the proposed permissions of 2'-FL and LNnT to

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<sup>16</sup> Brand name to be provided by the applicant.

any other food categories as our assessment has focussed specifically on infant formula products and FSFYC as requested in the application.

## **2.3 Risk communication**

### **2.3.1 Consultation**

Consultation is a key part of FSANZ's standards development process.

FSANZ has developed a communication strategy for this application. Subscribers and interested parties have been notified about this call for submissions via the FSANZ Notification Circular, media release and through FSANZ's social media tools and Food Standards News.

FSANZ acknowledges the time taken by individuals and organisations to consider this application. All comments are valued and contribute to the rigour of our assessment. Comments received will be taken into account when deciding whether to develop draft variation(s) at the next stage of assessment.

### **2.3.2 World Trade Organization (WTO)**

This issue will be fully considered at the next stage of the assessment and, if necessary, notification will be made in accordance with Australia's and New Zealand's obligations under either the WTO Technical Barriers to Trade (TBT) or Application of Sanitary and Phytosanitary Measures (SPS) Agreements. This will enable other WTO members to comment on any proposed amendments.

## **2.4 FSANZ Act assessment requirements**

When assessing this application, FSANZ has had regard to the following matters in section 29 of the FSANZ Act:

### **2.4.1 Section 29**

#### **2.4.1.1 Consideration of costs and benefits**

The Office of Best Practice Regulation (OBPR) exempted FSANZ from the need to undertake a formal Regulation Impact Statement (RIS) in relation to the regulatory change proposed in response to this application (OBPR correspondence dated 1 February 2018, reference 23349). This was due to OPBR being satisfied that the requested variation is voluntary and deregulatory and likely to have only a minor effect on consumers, businesses, and government.

FSANZ, however, has given consideration to the costs and benefits that may arise from the proposed measure for the purposes of meeting FSANZ Act considerations. FSANZ is required to have regard to whether costs that would arise from the proposed measure outweigh the direct and indirect benefits to the community, government or industry that would arise from the proposed measure (S.29(2)(a)).

The purpose of this consideration is to determine if the community, government, and industry as a whole is likely to benefit, on balance, from a move from the status quo. This analysis considered approving the requested addition of 2'-FL alone or combined with LNnT to infant formula products and FSFYC with variation as proposed by FSANZ.

FSANZ's preliminary view that no other realistic food regulatory measures exist, however information received may result in FSANZ arriving at a different outcome.

The consideration of the costs and benefits in this section is not intended to be an exhaustive, quantitative economic analysis of the proposed measures and, in fact, most of the effects that were considered cannot easily be assigned a dollar value. Rather, the assessment seeks to highlight the likely positives and negatives of moving away from the status quo by permitting the voluntary addition of 2'-FL alone, or in combination with LNnT, to infant formula products and FSFYC.

#### *Costs and benefits of permitting 2'-FL and LNnT as proposed*

The use of 2'-FL and LNnT in infant formula products and FSFYC as proposed will not pose a health or safety risk for consumers.

The proposed use may provide potential beneficial health outcomes for infants and toddlers as discussed in section 2.2.1. Consumers may therefore benefit from the choice of infant formula products and FSFYC containing 2'-FL alone or with LNnT that become available.

As the proposed permission is voluntary, industry will use 2'-FL alone or in combination with LNnT in infant formula products and FSFYC only where they believe a net benefit exists. Industry will benefit from having alternative options available to existing permitted non-digestible oligosaccharides (GOS and ITF).

The applicant's 2'-FL and LNnT is permitted for use in infant formula products and FSFYC in some overseas countries or regions including the EU and US. The proposed permission will enable Australian and New Zealand manufacturers to access and use ingredients that are available to their overseas competitors, which may provide trade opportunities. It could also result in competing imports from overseas markets into Australia and New Zealand.

Permitting 2'-FL and LNnT as proposed may result in a small cost to government in terms of monitoring and compliance as regulators will need to be aware of the permitted levels in infant formula products and FSFYC.

#### *Conclusion from cost benefit considerations*

FSANZ's assessment is that the direct and indirect benefits that would arise from permitting the voluntary addition of 2'-FL and LNnT in the manner proposed will most likely outweigh the associated costs.

FSANZ seeks comments on this assessment in order to inform a decision in relation to preparation of a draft variation

#### **2.4.1.2 Other measures**

FSANZ at this stage remains unaware of any measure which would be more cost effective than a food regulatory measure developed or varied as a result of the application. FSANZ seeks comments on this assessment to inform its decision on preparation of a draft variation.

#### **2.4.1.3 Any relevant New Zealand standards**

There are no relevant New Zealand Standards.

#### **2.4.1.4 Any other relevant matters**

Other relevant matters are considered below.

## **2.4.2 Subsection 18(1)**

FSANZ has also considered the three objectives in subsection 18(1) of the FSANZ Act during the assessment.

### **2.4.2.1 Protection of public health and safety**

FSANZ has completed a safety, technical and health effects assessment (SD1) which is summarised in section 2.1. The assessment concluded that there are no public health and safety concerns associated with the addition of 2'-FL alone or in combination with LNnT to infant formula products and FSFYC at the requested levels, or at higher estimated levels of dietary intakes based on 2.4 g/L 2'-FL.

### **2.4.2.2 The provision of adequate information relating to food to enable consumers to make informed choices**

Should the voluntary addition of 2'-FL and LNnT be permitted as proposed for infant formula products and FSFYC, the existing and proposed labelling provisions discussed in section 2.2.5 would provide information to enable consumers make an informed choice.

### **2.4.2.3 The prevention of misleading or deceptive conduct**

Current labelling requirements, which aim to prevent misleading or deceptive conduct, would apply to the proposed permission.

## **2.4.3 Subsection 18(2) considerations**

FSANZ has also had regard to:

- **the need for standards to be based on risk analysis using the best available scientific evidence**

FSANZ has used the best available scientific evidence to assess this application. The applicant submitted a dossier of scientific studies as part of its application. Other relevant information including scientific literature was also used in assessing the application.

- **the promotion of consistency between domestic and international food standards**

The applicant's 2'-FL and LNnT are permitted for use overseas, including in the US and EU. Permitting 2'-FL and LNnT as proposed by FSANZ will promote greater compatibility between domestic and overseas food standards for infant formula products and FSFYC as discussed in section 2.2.3. The proposed specifications are essentially identical to those approved in the US and EU.

- **the desirability of an efficient and internationally competitive food industry**

The proposed permission would support an internationally competitive food industry for infant formula products and FSFYC.

- **the promotion of fair trading in food**

No negative impact is anticipated on fair trading.

- **any written policy guidelines formulated by the Forum on Food Regulation**

Two Ministerial Policy Guidelines apply to this application:

- *Regulation of Infant Formula Products*
- *Intent of Part 2.9 – Special Purpose Foods*

FSANZ considers that these policy guidelines have been met. Our assessment against these policy guidelines is provided at SD2.

### 3 References

EU (2017a) [Commission Implementing Regulation \(EU\) 2017/2470](#) of 20 December 2017 establishing the Union list of novel foods in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council of novel foods. Accessed 17 September 2018.

EU (2017b) [Commission Implementing Decision \(EU\) 2017/2201](#) of 27 November 2017 authorising the placing on the market of 2'-fucosyllactose produced with Escherichia coli strain BL21 as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council (notified under document C(2017) 7662). Accessed 17 September 2018

FSANZ (2008) Proposal P306, Final Assessment Report, Addition of Inulin/FOS & GOS to Food. Food Standards Australia New Zealand.

FSANZ (2013) Application A1055, Approval Report, Short Chain Fructo-oligosaccharides. Food Standards Australia New Zealand.

Israel MOH (2017) Novel Food Guidance on: Oligosaccharide 2'-fucosyllactose of January 16 2017. Ministry of Health, Food Control Services.

MEB (2017a) 2'-Fucosyllactose (2), Assessment of substantial equivalence for a notification, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients. Novel Foods Unit, Medicines Evaluation Board (MEB).

MEB (2017b) 2'-Fucosyllactose (3), Assessment of substantial equivalence for a notification, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients. Novel Foods Unit, MEB.

Singapore (2018) Sale of Food Act (Chapter 283, Section 56(1)) Food Regulations. Agri-Food & Veterinary Authority of Singapore. Version in force from 28/3/2018.

### Attachments

- A. Units basis for expressing maximum permitted amounts



# Attachment A – Units basis for expressing maximum permitted amounts

## 1 Infant formula products

Existing compositional requirements for infant formula products regulated in Standard 2.9.1 and Schedule 29 of the Code are primarily based on mg/100 kJ units. For consistency with existing provisions, FSANZ proposes to base the maximum amounts of 2'-FL and LNnT permitted for use in infant formula products on mg/100 kJ units as follows:

- If only 2'-FL added – no more than 96 mg/100 kJ of 2'-FL
- If both 2'-FL and LNnT added – no more than 24 mg/100 kJ of LNnT; and no more than 96 mg/100 kJ of 2'-FL and LNnT combined.

The minimum energy content of 2500 kJ/L currently permitted for infant formula and follow-on formula in the Code (section 2.9.1—9) was used to convert the proposed g/L amounts (i.e. 2.4 g/L of 2'-FL alone; and 2.4 g/L of 2'-FL and LNnT combined, with no more than 0.6 g/L LNnT) to mg/100 kJ.

This approach based on mg/100 kJ would mean that the actual amount of 2'-FL and LNnT in infant formula products could vary depending on the energy content of the formula. In particular, a formula with a higher energy content per 100 mL may contain more 2'-FL, or more 2'-FL and LNnT, than a formula with a lower energy content. However, where a formula has a higher energy content, less formula would need to be consumed to meet infant energy requirements. Conversely, more would need to be consumed to meet infant energy requirements for a formula with a lower energy content. As such, the respective dietary intakes for 2'-FL and LNnT would be similar for formulas with varying energy contents as the amount of formula consumed is regulated by infant energy needs.

FSANZ's dietary intake assessment (SD1) estimated the respective dietary intakes of 2'-FL and LNnT from infant formula and follow-on formula (for infants aged 3 and 9 months respectively), using the proposed amounts in mg/100 kJ units listed above. As discussed in section 2.1.1, the estimated intake of 2'-FL was similar to the intakes from 3 and 9 month old breastfed infants. Although the estimated intake of LNnT was higher than those for 3 and 9 month old breastfed infants (based on the mean concentration present in human milk), the proposed maximum use level is within the range of concentrations naturally present in human milk (i.e. 0.09 – 1.08 g/L). Additionally, the highest P90 intakes estimated for 2'-FL and LNnT respectively, were well below the no observable adverse effect level (NOAEL) identified by FSANZ in SD1 (i.e. 7-fold lower for 2'-FL, and 30-fold lower for LNnT, for 3 month old infants).

Based on the conclusions of FSANZ's safety, technical and health assessment, and noting the range of 2'-FL and LNnT concentrations naturally present in human milk, FSANZ considers that the proposed maximum permitted amounts based on mg/100 kJ are unlikely to pose a risk to infant health.

## 2. Formulated supplementary foods for young children

Existing permissions in Division 4 of Standard 2.9.3 and Schedule 29 for the addition of substances to FSFYC are on a per serving basis. For consistency with existing permissions, FSANZ proposes to base the maximum amounts of 2'-FL and LNnT permitted for use in FSFYC on g/serving units as follows:

- If only 2'-FL added – no more than 0.56 g/serving
- If both 2'-FL and LNnT added – no more than 0.14 g/serving of LNnT; and no more than 0.56 g/serving of 2'-FL and LNnT combined.

A 230 mL serve size was used for the conversion from the proposed maximum g/L amounts to g/serving. According to the applicant, and an online search of FSFYC products by FSANZ, this is the largest serve size currently used in the Australia and New Zealand FSFYC market.

'Serving' is defined in Standard 1.1.2 – Definitions used throughout the Code<sup>17</sup>. The serving size is determined by the food manufacturer and must be declared in the nutrition information panel (Standard 1.2.8). The proposed permission in the Code would therefore specify the permitted amounts per serve (as listed above), but would not specify the serving size. This means that the permitted amounts per serving would be the same irrespective of the serving size (e.g. maximum of 0.56 g of 2'-FL per 115 mL serving and per 230 mL serving).

FSANZ's dietary intake assessment (SD1), estimated the respective dietary intakes of 2'-FL and LNnT from FSFYC (for 12 month old infants and 2–3 year old children) using the proposed amounts based on g/serving listed above. In the modelling, two FSFYC serving sizes were used to provide a range of estimated intakes (i.e. smallest serve of 115 mL and largest serve of 230 mL as currently available in the Australia and New Zealand market). The smaller FSFYC serving size resulted in higher intakes of 2'-FL and LNnT respectively, as more servings would need to be consumed to meet the energy needs of an older infant and young child.

As discussed in section 2.2.3.2 of this report, the estimated intakes from FSFYC are similar to or less than the respective intakes of 2'-FL and LNnT for 3 month old infants who are exclusively formula-fed and are a more vulnerable population group. The highest P90 intakes of 2'-FL and LNnT from FSFYC are also well below the NOAEL's identified by FSANZ in SD1 (i.e. 12-fold lower for 2'-FL, and 50-fold lower for LNnT, for 12 month old infants).

As there are no safety concerns identified with the proposed addition of 2'-FL and LNnT to FSFYC, FSANZ considers that the maximum levels based on g/serving are unlikely to pose a risk to the health of young children.

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<sup>17</sup> *Serving* means an amount of the food which constitutes one normal serving when prepared according to manufacturer's directions or when the food requires no further preparation before consumption, and in the case of a formulated meal replacement is equivalent to one meal.