8 June 2023
245-23

Call for submissions – Application A1265

A1265 – 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products

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Food Standards Australia New Zealand (FSANZ) has assessed an Application made by Glycom A/S to amend the Australia New Zealand Food Standards Code to permit the voluntary addition of 2'-fucosyllactose (2'-FL) and difucosyllactose (DFL) (2'-FL/DFL), lacto-N-tetraose (LNT), 6'-sialyllactose sodium salt (6'-SL) and/or 3'-sialyllactose sodium salt (3'-SL) as nutritive substances in infant formula products and has prepared a draft food regulatory measure. Pursuant to section 31 of the *Food Standards Australia New Zealand Act 1991* (FSANZ Act), FSANZ now calls for submissions to assist consideration of the draft food regulatory measure.

For information about making a submission, visit the FSANZ website at current calls for public comment and how to make a submission.

All submissions on applications and proposals will be published on our website. We will not publish material that we accept as confidential. In-confidence submissions may be subject to release under the provisions of the *Freedom of Information Act 1982*. Submissions will be published as soon as possible after the end of the submission period.

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.

For information on how FSANZ manages personal information when you make a submission, see FSANZ's Privacy Policy.

Submissions should be made in writing; be marked clearly with the word 'Submission'. You also need to include the correct application or proposal number and name. Electronic submissions can be made by emailing your submission to submissions@foodstandards.gov.au. FSANZ also accepts submissions in hard copy to our Australia and/or New Zealand offices.

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) 7 July 2023

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 a submission or application and proposal processes can be sent to standards.management@foodstandards.gov.au.

Submissions in hard copy may be sent to the following addresses:

Food Standards Australia New Zealand
PO Box 5423
KINGSTON ACT 2604
AUSTRALIA
Tel +61 2 6271 2222

Food Standards Australia New Zealand
PO Box 10559
WELLINGTON 6140
NEW ZEALAND
Tel +64 4 978 5630

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Supporting document

The following document which informed the assessment of this Application are available on the FSANZ website:

SD1 Risk assessment – Application A1265

Executive summary

Food Standards Australia New Zealand (FSANZ) has assessed Application A1265 made by Glycom A/S (the Applicant) to amend the Australia New Zealand Food Standards Code (the Code) to permit the voluntary addition of four human-identical milk oligosaccharide products for use as nutritive substances in infant formula products (IFP)[1]. The substances are produced by microbial fermentation using a genetically modified strain of *Escherichia coli* K-12. The substances and their proposed maximum permitted amounts are:

- A mixture of 2'-fucosyllactose (2'-FL) and difucosyllactose (DFL) (2'-FL/DFL) (96 mg/100 kJ);
- lacto-N-tetraose (LNT) (32 mg/100 kJ);
- 6'-sialyllactose sodium salt (6'-SL) (16 mg/100 kJ); and
- 3'-sialyllactose sodium salt (3'-SL) (8 mg/100 kJ).

The Applicant has also requested an exclusive use permission for their brand of each substance for a period of 15 months after gazettal.

FSANZ's safety and technical assessment concluded that there are no public health and safety concerns associated with adding the substances to IFP at the levels requested, which are comparable to levels in human milk and are chemically and structurally identical to the naturally occurring forms.

In accordance with the relevant Ministerial Policy Guidelines[2], FSANZ's assessment of beneficial health effects and intended purpose concluded that the use of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL, individually or in combination in IFP, would have a beneficial outcome for infants and align with the equivalent role of these substances in human milk. The weight of evidence supports health effects of 2'-FL/DFL, LNT, 6'-SL and 3'-SL added to infant formula through an increase in the abundance of *Bifidobacterium* spp. in the infant gut microbiota, anti-pathogenic effects, inflammatory suppression and facilitation of appropriate immune responses and antigenic memory.

FSANZ has prepared a draft variation to the Code to permit the voluntary addition for each of 2'-FL/DFL, LNT, 6'-SL and 3'-SL to be *used as a nutritive substance* and as *food produced using gene technology* in IFP. If approved, the draft variation would:

- amend Schedule 29 of the Code to permit 2'-FL/DFL, LNT, 6'-SL and 3'-SL to be used in infant formula products, either alone or in combination, as a nutritive substance up to a specified maximum permitted amount;
- amend Schedule 26 of the Code to permit 2'-FL/DFL, LNT, 6'-SL and 3'-SL, as substances derived from a new genetically modified microbial source, to be added to infant formula products subject to certain conditions, including an exclusive use period of 15 months for the applicant's brand of each substance;
- amend Schedule 3 of the Code to include identity and purity specifications for the 2'-FL/DFL, LNT, 6'-SL and 3'-SL; and

[1] Includes infant formula, follow-on formula and infant formula products for special dietary purposes.

[2] Policy guideline on infant formula products and Policy guideline on intent of Part 2.9 of the Food Standards Code - special purpose foods.

- remove the current prohibition in Standard 2.9.1 on the use of galacto-oligosaccharides and/or inulin-type fructans with lacto-N-neotetraose.

Removal of the prohibition on use of GOS and/or IFT with LNnT in IFP

The draft variation prepared by FSANZ, if approved, would also remove the current prohibition in Standard 2.9.1 on the addition to IFP of galacto-oligosaccharides (GOS) and/or inulin-type fructans (IFT) in combination with lacto-N-neotetraose (LNnT). Removal of the prohibition was not requested by the Applicant. However, FSANZ considers this proposed amendment to be warranted for the reasons listed in this report. It will, for example, provide regulatory clarity and allow greater flexibility in combinations of oligosaccharides in IFP.

FSANZ now seeks submissions on the draft variation (Attachment A).

1 Introduction

1.1 The Applicant

The Applicant Glycom A/S is a Danish food ingredient manufacturer who specialises in the development, synthesis and commercialisation of human-identical milk oligosaccharides[3] (HiMO) substances.

1.2 The Application

Glycom A/S seek to amend Standard 2.9.1 and Schedules 3, 26 and 29 of the Australia New Zealand Food Standards Code (the Code) to permit the voluntary addition of four HiMO products for use as nutritive substances in infant formula products[4] (IFP). The substances are produced by microbial fermentation using a genetically modified strain of *Escherichia coli* K-12. The substances and their proposed maximum permitted amounts are:

- a mixture of 2'-fucosyllactose (2'-FL) and difucosyllactose (DFL) (2'-FL/DFL) (96 mg/100 kJ);
- lacto-N-tetraose (LNT) (32 mg/100 kJ);
- 6'-sialyllactose sodium salt (6'-SL) (16 mg/100 kJ); and
- 3'-sialyllactose sodium salt (3'-SL) (8 mg/100 kJ).

2'-FL/DFL, LNT, 6'-SL and 3'-SL are non-digestible oligosaccharides that are components of human milk. The Applicant is seeking to add its 2'-FL/DFL, LNT, 6'-SL, and 3'-SL individually or in combination, as nutritive substances to IFP.[5] The substances are not expressly permitted by the Code for use as nutritive substances, and as per paragraph 1.1.1—10(6)(b) of Standard 1.1.1, require pre-market assessment.

1.3 The current Code requirements

Australian and New Zealand food laws require food for sale to comply with relevant provisions in the Code. The provisions that are relevant to this Application are summarised below.

1.3.1 Infant formula products

The composition and labelling of IFP is regulated in Standard 2.9.1 and Schedule 29. They set out specific compositional and labelling requirements for the following IFP:

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

1.3.2 Permitted use

Food produced using gene technology

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

[3] The term "HiMO" is used in this CFS to refer generically to human identical milk oligosaccharides when relevant. It is not intended to indicate or infer that the term is appropriate or approved to be used in labelling IFP.
[4] Includes infant formula, follow-on formula and infant formula products for special dietary purposes.
[5] IFP: infant formula, follow-on formula and infant formula for special dietary use.

ingredient or component a *food produced using gene technology*. The four substances are each considered a *food produced using gene technology* (section 1.1.2—2) having been derived from an organism modified using gene technology (i.e. derived from genetically modified (GM) *E.coli* strains). If approved, express permission for 2'-FL/DFL, LNT, 6'-SL and 3'-SL produced using *Escherichia coli (E.coli)* K-12 is required in accordance with Standard 1.5.2 (i.e. to be listed in Schedule 26 and to comply with any corresponding conditions).

Nutritive substances

In addition, paragraph 1.1.1—10(6)(b) of Standard 1.1.1 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* (as defined in section 1.1.2—12).

FSANZ considers the four substances to be nutritive substances because their addition to food is intended to achieve specific nutritional purposes (as per the stated definition of a nutritive substance in section 1.1.2—12 of the Code). The Applicant has demonstrated this in accordance with the requirements in the FSANZ Application Handbook (section 3.3.3). Therefore, if approved, an express permission for 2'-FL/DFL, LNT, 6'-SL and 3'-SL to be *used as a nutritive substance* is required in section S29—5 in addition to the permission as *food produced using gene technology* above.

1.3.3 Identity and purity

Section 1.1.1—15 requires that a substance that is *used as a nutritive substance* must comply with any relevant identity and purity specification set out in Schedule 3. Schedule 3 currently only lists two specifications for HiMO: 2′-FL and lacto-N-neotetraose (LNnT). 2′-FL has been assessed in Applications A1155, A1190 and A1233 (FSANZ 2019; FSANZ 2021a; FSANZ 2022). Application A1155 assessed permitting both 2′-FL and LNnT in infant formulas and other products.

1.3.4 Labelling requirements

Subsection 1.1.1—10(8) requires that food for sale must comply with all relevant labelling requirements in the Code for that food.

Section 1.2.4—2 requires food products to be labelled with a statement of ingredients. Section 1.2.4—4 requires ingredients to be declared using: a name by which they are commonly known; a name that describes their true nature; or a generic ingredient name if one is specified in Schedule 10.

Standard 1.2.7 sets out the requirements and conditions for voluntary nutrition content and health claims made about food. Paragraph 1.2.7—4(b) states a nutrition content claim or health claim must not be made about an IFP.

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*[6] (GM food).

Subparagraph 2.9.1—21(1)(a)(iii) of Standard 2.9.1 requires the average amount of any substance used as a nutritive substance permitted by Standard 2.9.1 to be declared in the

[6] Section 1.5.2—4(5) defines ***genetically modified food*** to mean a '*food produced using gene technology that
a) contains novel DNA or novel protein; or
b) is listed in Section S26—3 as subject to the condition that its labelling must comply with this section' (*that being section 1.5.2—4*).

nutrition information statement (NIS), expressed in weight/100 mL. Paragraphs 2.9.1—24(1)(ca) and (cb) prohibit the use of: the words 'human milk oligosaccharide', 'human milk identical oligosaccharide';the abbreviations 'HMO' or 'HiMO';or any words and abbreviations having the same or similar effect. Paragraph 2.9.1—24(1)(f) prohibits a reference to the presence of a nutrient or substance that may be used as a nutritive substance, except for a reference in: a statement relating to lactose under subsection 2.9.1—14(6); a statement of ingredients; or in the NIS.

1.3.5 Current oligosaccharide permissions and restrictions

2'-FL and LNnT are permitted to be *used as a nutritive substance* in IFP in accordance with section 2.9.1—5, with forms permitted for use being listed in the table to section S29—5. All 2'-FL and LNnT currently permitted by the Code are chemically and structurally identical to those found in human milk.

In conjunction with the Schedule 29 permissions, subsection S26—3(7) permits 2′-FL and LNnT as *foods produced using gene technology of microbial origin* with microbial sources and conditions as listed. This includes the Applicant's 2′-FL produced by microbial fermentation from genetically modified (GM) *E coli* K-12 containing the gene for alpha-1,2-fucosyltransferase from *Helicobacter pylori*. However, the Code does not currently permit 2'-FL as a mixture with DFL.

Schedule 3 provides specifications for the permitted oligosaccharides.

Section 2.9.1—7 of the Code regulates the addition of galacto-oligosaccharides (GOS) and inulin-type fructans (ITF) (both are defined in subsection 1.1.2—2(3)) to IFP (see section 2.9.1—7). GOS and ITF 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). ITF are not present in human milk and GOS is found only in trace amounts (FSANZ 2008).

For IFP, section 2.9.1—7 sets out restrictions on the addition of ITF and GOS.

Subsection 2.9.1—7(1) 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. Subsection 2.9.1—7(2) prohibits the use of ITF and/or GOS in IFP with lacto-N-neotetraose (LNnT)[7]. Subsection 2.9.1—7(3) permits 2′-FL to be used in combination with ITF and/or GOS. An exclusive use period[8] is current and requires that IFP which contains 2′-FL in combination with ITF and/or GOS may only be sold if the IFP is the prescribed IFP[9] manufactured by Nutricia Australia Pty. Ltd.

[7] Recent Application A1251 removed this prohibition from applying to 2′-FL.
[8] Exclusive use period means the period commencing on the date of gazettal of the *Food Standards (Application A1251 – 2'-FL combined with galactooligosaccharides and/or inulin-type fructans in infant formula products) Variation* and ending 15 months after that date.
[9] The prescribed infant formula product: (i) is manufactured by Nutricia Australia Pty. Ltd.; and (ii) contains, as a nutritive substance, 2′-fucosyllactose sourced from Escherichia coli BL21 containing the gene for alpha-1,2-fucosyltransferase from Escherichia coli O126; and (iii) contains Nutricia Australia Pty Ltd's blend of short-chain galactooligosaccharides and long chain fructo oligosaccharides, namely scGOS/lcFOS (9:1).

1.4 International standards

In developing food regulatory measures, FSANZ must have regard to the promotion of consistency between domestic and international food standards.

Internationally, 2'-FL/DFL, LNT, 6'-SL and 3'-SL, produced through microbial fermentation and by chemical synthesis, are permitted for use in infant formula equivalent products and a number of general foods at a range of levels and in combination with other oligosaccharides.

Codex Alimentarius (Codex) International Food Standards do not currently exist for 2'-FL/DFL, LNT, 6'-SL nor 3'-SL. However, the Codex Standards for 'Infant Formula and Formulas for Special Medical Purposes Intended for Infants' (Codex Alimentarius 2020) and for 'Follow-Up Formula' (Codex Alimentarius 2017) contain provisions for 'optional ingredients' which are applicable to 2′-FL/DFL, LNT, 6'-SL and 3'-SL.

2′-FL produced by microbial fermentation and by chemical synthesis are permitted for use in IFP and/or formulated supplementary foods for young children (also known as 'toddler milks') in at least 37 overseas countries including the United States, Canada, Singapore, the European Union, Israel, Korea and the Philippines.

In the European Union (EU), 2'-FL/DFL, LNT, 6'-SL and 3'-SL are authorised as novel food ingredients for foods including infant formula and follow on formula (EU 2019, 2020, 2021a,b).

The Applicant's 2'-FL/DFL, LNT, 6'-SL, and 3'-SL in infant formula and other products have been notified as GRAS (Generally Recognised as Safe) in the United States, with a US Food and Drug Administration (FDA) no questions letter (U.S. FDA, 2019a,b, 2020a,b).

In Singapore, 2'-FL/DFL, LNT, 6'-SL and 3'-SL have been authorised for use by the Singapore Food Agency (SFA). Permitted conditions of use of 2'-FL/DFL and LNT in infant formula were gazetted in the most recent amendment of the Food Regulations (SSO 2021), while 6'-SL and 3'-SL will be included in the next planned amendment of the Food Regulations (approval letters were provided to FSANZ in-confidence).

In Israel, the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL are permitted as novel foods for which provisions are laid down in New Food Directives from the National Food Service Guidelines List (Israel MOH, 2022 a, b, c, d).

In Brazil, the Applicant's LNT, 6'-SL and 3'-SL have been authorised for use by the Brazilian Health Regulatory Agency (approval letters provided in-confidence).

FSANZ notes that another manufacturer of HiMO substances has recently gained EU approval for LNT, 3-fucosyllactose (3'-FL), 6'-SL and 3'-SL to be used in infant formula products and other foods.[10]

1.5 Reasons for accepting Application

The Application was accepted for assessment because:

[10] Infant formula HMOs get EU novel food approval (foodprocessing.com.au).

- it complied with the procedural requirements under subsection 22(2) of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act); and
- it related to a matter that warranted the variation of a food regulatory measure.

1.6 Procedure for assessment

The Application is being assessed under the General Procedure.

2 Summary of the assessment

2.1 Risk assessment

FSANZ has undertaken an assessment of the food technology aspects, safety, nutritional impact and beneficial health effects of the addition of 2′-FL/DFL, LNT, 6′-SL and 3′-SL to IFP.

Information reviewed in the food technology assessment demonstrated the Applicant's 2′-FL/DFL, LNT, 6′-SL and 3′-SL were chemically and structurally identical to the naturally occurring forms of these substances in human milk. The substances were shown to be stable in infant formula products (IFP) with an adequate shelf-life. Multi-batch analyses showed the oligosaccharides can be consistently produced to meet their proposed specifications.

The *E. coli* K-12 host organism has a long history of use for the production of recombinant proteins and poses no risks to humans. Analyses of the gene donors also confirmed there are no safety concerns. The production strains were genetically and phenotypically stable.

Mean estimated dietary intakes of 2′-FL, DFL, LNT, 6′-SL and 3′-SL from IFP were comparable to mean estimated dietary intakes from mature human milk. High (90th percentile) estimated dietary intakes from IFP did not exceed estimated dietary intakes from mature human milk at high consumption and high concentration levels, except for DFL when assuming a representative maximum composition of 25% in the proposed 2′-FL/DFL mixture. The maximum composition of 25% for DFL is the most conservative concentration, and is markedly higher compared to the mean composition from analysis provided by the Applicant (12%). Based on the mean analysed concentration of DFL, the estimated mean intakes, which are more reflective of longer term intakes, from IFP are similar to that from human milk.

Based on the available toxicological and clinical data, also considering the dietary intake assessment, it was concluded that there were no public health and safety concerns associated with the addition of the Applicant's 2′-FL/DFL, LNT, 6′-SL and 3′-SL to IFP at the proposed use amounts. No microbiological safety concerns were identified.

Post-marketing surveillance data have also found no safety concerns following consumption of infant formula containing a combination of the Applicant's 2′-FL/DFL, LNT, 6′-SL and 3′-SL.

The weight of evidence supports health benefits of HiMOs added to IFP through an increase in the abundance of *Bifidobacterium spp.* in the infant gut microbiota, anti-pathogenic effects, inflammatory suppression and facilitating appropriate immune responses and antigenic memory. The inclusion of a wider range of HiMOs to IFP enables the microbiota profile to more closely resemble that of breastfed infants.

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 when breastfeeding is not possible. As infants are a vulnerable population group, infant formula products (IFP) are regulated by prescriptive provisions for composition and labelling. Any changes to the composition of these products must be established as safe prior to being permitted.

2.2.1 Risk management options

The risk management options available to FSANZ after assessment were to either:

- reject the Application, or
- prepare a draft variation of the Code.

For the reasons set out in this Report, FSANZ has prepared a draft variation to the Code to permit the use of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL as nutritive substances in IFP, subject to certain conditions. If approved, the proposed permissions would have to be exercised in accordance with the Code.

Further details on the proposed permission and associated proposed conditions are provided below. FSANZ has had regard to the requirements of the FSANZ Act (see Section 2.4 below) in developing the draft variation.

2.2.2 Use as a nutritive substance in IFP

There are more than 200 human milk oligosaccharides (HMOs) in human milk and a large accumulating body of evidence demonstrating their role in the normal growth and development of infants, in particular to aid in the maturation of the infant microbiota. In human milk, 10 individual HMOs make up over 70% of total HMO concentration (Soyyılmaz et al. 2021). Recent innovation has seen the synthesis of these primary oligosaccharides biochemically identical to HMOs, such as those requested by the Applicant.

The safety, technical and health effects assessment (SD1) concluded that there are no public health and safety concerns associated with the addition of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL in IFP at the levels proposed, which are comparable to that of human milk.

FSANZ's assessment of potential health effects of 2'-FL/DFL, LNT, 6'-SL and 3'-SL was consistent with assessments undertaken previously for the same types of substances. In previous applications (A1155, A1190 and A1233) FSANZ considered the weight of available evidence when assessing the beneficial role of 2'-FL and LNnT in the normal growth and development of infants.

While data from well-controlled human studies are considered of greatest value, ethical constraints limit their availability when considering health outcomes from interventions in infants and children. In the absence of this data, and in order to fully consider benefit, evidence from non-human studies is used to add weight to the determination of a substance's role, particularly in understanding the mode of action and biological plausibility. In assessing a link between the relevant physiological, biochemical or functional effects impact of a substance in infant formula and specific health effects in infants, FSANZ deems it appropriate to consider an evidence base that includes animal studies, *in vitro* evidence and relevant observational and/or epidemiological studies. FSANZ refers to the assessment from the Independent Expert Advisory Group (IEAG) undertaken under Application A1155, who

similarly concluded that there are many different factors in the microbiome which influence infant health, and that it is not possible to determine a linear effect from the presence of one substance in human milk and a specific health outcome (FSANZ 2020). Referring also to Section 2.1 of this CFS, development of a microbiota profile closer to that of breastfed infants is supported by inclusion of a wider range of HiMOs.

The nutritional purpose for adding 2'-FL/DFL, LNT, 6'-SL and 3'-SL to IFP is to create products that better reflect the oligosaccharide profile of human milk. A demonstrable health outcome in conjunction with bringing the composition of IFP closer to that of human milk is aligned with the definitions of infant formula and follow-on formula in the Code and reflects the primary purpose of consumption in supporting the development of infants that cannot be breastfed. In line with specific policy principle (j)[11], FSANZ has considered these requirements in assessing each of the beneficial health effects of the Applicant's substances stated in the Application: anti-pathogenic effect; bifidogenic effect; and immunomodulation.

Based on FSANZ's assessment of beneficial health effects and role in normal growth and development, and taking a weight of evidence approach, FSANZ concludes that the use of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL, individually or in combination, would have a beneficial outcome.

2.2.3 Permission in the Code

In permitting 2'-FL/DFL, LNT, 6'-SL and 3'-SL as proposed above, express permission would be provided for each of 2'-FL/DFL, LNT, 6'-SL and 3'-SL 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, individually or in combination, derived from the Applicant's GM production strains.

2'-FL and DFL are two distinct fucosylated HMOs that are always found together in human milk. They are structurally and biologically closely related since DFL is metabolically obtained from 2'-FL by the addition of a second fucose unit ("fucosylation"). In this Application, 2'-FL and DFL are produced in the same fermentation and are isolated together to produce the 2'-FL/DFL mixture.

Listing LNT, 6'-SL and 3'-SL and the combination of 2'-FL with DFL as individual permissions in section S29—5 is consistent with how 2'-FL and 2'-FL/LNnT are currently listed in the Code, with permission for the GM organism in accordance with Standard 1.5.2. Single entry permissions allows for more efficient assessments of future applications for HiMO-type ingredients. FSANZ considers the approach to permit single oligosaccharides as minimum effective regulation.

The proposed permission also supports international consistency and a competitive food industry (high order policy principles 2(b) and (c)[12]), providing trade opportunities. In countries where permissions exist (e.g. Singapore, EU, United States), 2'-FL/DFL, LNT, 6'-SL and 3'-SL are permitted as single ingredients in IFP (refer Section 1.4).

2.2.4 Use with GOS and ITF

GOS and ITF have been permitted for addition to IFP since the gazettal of Proposal P306 in 2008, to emulate the effects of HMO and strive to achieve as closely as possible the normal

[11] Policy guideline on infant formula products.
[12] Policy guideline on infant formula products.

growth and development of infants. As noted in Section 1.3.5 above, ITF is not present in human milk, and GOS only in trace amounts. At the time of approval of P306, ITF and GOS were the only available form of non-digestible oligosaccharides. While systems to synthesise oligosaccharides biochemically identical to HMOs are becoming more widespread, this technology remains expensive and if used as the sole source of oligosaccharides in IFP, could result in prohibitive IFP prices for consumers.

In Application A1155, based on the available evidence, and given the combined use of the proposed and existing permissions was not requested, FSANZ decided to prohibit the combination of 2'-FL alone or with LNnT in combination with GOS and/or ITF in IFP. At that time, it was considered that an application with appropriate supporting evidence would have been required to allow consideration of such oligosaccharide combinations.

More recently under Application A1251, FSANZ assessed the combination of 2'-FL, GOS and ITF substances in IFP. FSANZ's risk and technical assessment identified no public health and safety concerns with the combination of 2′-FL with GOS and/or ITF in IFP at current permitted maximum use amounts (FSANZ 2022a). Taking into account the A1251 assessment, FSANZ is not proposing to prohibit the use of GOS and/or ITF in combination with 2'-FL/DFL, LNT, 6'-SL and/or 3'-SL.

2.2.5 Total oligosaccharide amounts and cumulative effect

This Application, if approved, will add permissions for four new oligosaccharides to IFP. These will be permitted to be added either as single ingredients (2'FL/DFL, LNT, 6'-SL and 3'-SL) or as a mixture (see Table 1). The proposed maximum amounts for each are consistent with the concentrations of these individual oligosaccharides in human milk (refer to Section 4.5 of SD1). In terms of the total amount of HMOs to be added, the combined maximum amount of 2'-FL or 2'-FL/LNnT or 2'-FL/DFL, LNT, 6'-SL and 3'-SL would total 0.15 g/100 kJ added to IFP. This amount is less than the lower limit of average total oligosaccharide concentration reported in mature human milk (10 – 15 g/L or 0.34 – 0.51 g/100 kJ[13]), as reported by Zhang et al. (2021). As the oligosaccharides listed in Table 1 represent the most abundant HMOs in mature human milk (Soyyilmaz et al. 2021), it is unlikely that the additional permissions requested in this Application, or in future applications, would exceed concentrations in human milk.

Including the maximum amount permitted for ITF and GOS would equal 0.55 g/100 kJ of total added oligosaccharides. However, as noted above, the technology to produce HMOs remains expensive but as biochemically identical HMOs become more available, ITF and GOS will become unnecessary in IFP. In future applications, FSANZ can consider setting a maximum amount for total added oligosaccharides, if warranted. At this time, such a regulatory measure would (1) not be supported by FSANZ safety assessments conducted to date and (2) potentially place Australia and New Zealand out of step with international regulations.

Table 1: Summary of IFP oligosaccharide permissions including those proposed in this Application

Oligosaccharide	Maximum amount (mg/100 kJ)	Amount expressed as %Energy
2'-FL or 2'-FL/LNnT or 2'-FL/DFL	96	0.8
LNT	32	0.3

[13] Amount in g/100 kJ is calculated using the energy density reported in AUSNUT (FSANZ 2016): 286 kJ/100 g = 297 kJ/100 mL based on the specific gravity of human milk of 1.04 g/mL.

6'-SL	16	0.1
3'-SL	8	0.1
Total HiMO	152	1.2
ITF	110	0.9
GOS	290	2.3
Total oligosaccharides	552	4.4

Based on the permissions listed in Table 1, total added oligosaccharides would be a small fraction of the total carbohydrate content. Total carbohydrate content is calculated by difference based on the prescribed range of fat and protein, and the energy density. The calculated carbohydrate range in infant formula expressed as a percentage of the energy density is 36 – 52%. The calculated amount of oligosaccharides expressed as a percentage of the energy density would be 1.2% for HiMOs only, and 4.4% if ITF and GOS are included, which is a fraction of the total range of carbohydrate content.

Based on the proposed changes, these calculations demonstrate that the potential cumulative increase to the total oligosaccharide load consumed by infants is aligned with human milk, poses no safety or public health risks, and complies with longstanding total carbohydrate permissions. Details of the above calculations are provided at Appendix 1.

2.2.6 Removal of the prohibition on the use of ITF and/or GOS with LNnT

The draft variation prepared by FSANZ for this Application would also remove the current prohibition imposed by subsection 2.9.1—7(2) on the use of ITF and/or GOS in IFP with LNnT. Removal of the prohibition was not requested by the Applicant. LNnT is a HMO and is permitted to be added to IFP at concentrations consistent with human milk. LNnT has no known chemical or biological characteristics different from other permitted HMOs that would lead to adverse outcomes in infants. Consistent with FSANZ's assessment for the removal of the prohibition for 2'-FL with ITF and/or GOS (see Application A1251), FSANZ is satisfied that there are no public health and safety concerns with the combination of ITF and/or GOS in IFP with LNnT at current permitted maximum use amounts. FSANZ considers this amendment reflects the scientific evidence, provides regulatory clarity and also allows for greater flexibility in combinations of oligosaccharides in IFP.

2.2.7 Specification

Section 1.1.1—15 requires *a substance that is used as a nutritive substance* must comply with any relevant specification set out in Schedule 3. Since no published specifications currently exist for 2'-FL/DFL, LNT, 6'-SL and 3'-SL in Schedule 3, FSANZ proposes adopting the specifications proposed by the Applicant.

The proposed specification parameters are shown in Tables 1 to 4 of SD1. These specifications are included in the draft variation at Attachment A.

2.2.8 Labelling

2.2.8.1 Statement of ingredients

Standard 1.2.4 requires food for sale to be labelled with a statement of ingredients unless exempt. The label on a package of IFP must contain a statement of ingredients. Should manufacturers choose to add 2'-FL/DFL, LNT, 6'-SL and 3'-SL individually or in combination, then these substances must 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; 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*.

The existing generic ingredient labelling requirements would apply to the permitted forms of 2'-FL/DFL, LNT, 6'-SL and 3'-SL, enabling industry to have flexibility in how they declare these ingredients (for example, using the names '2′-fucosyllactose' and '6'-sialyllactose sodium salt'). Noting however the existing prohibited representations in paragraphs 2.9.1—24(1)(ca) and (cb) (refer to section 2.2.8.3 below) would also apply.

2.2.8.2 Mandatory nutrition information

Section 2.9.1—21 regulates the declaration of nutrition information in a nutrition information statement (NIS) on the label of IFP. The NIS is a single statement and may be in the form of a table, as indicated in Section S29—10 *Guidelines for Infant Formula Products*.

Subparagraph 2.9.1—21(1)(a)(iii) requires the average amount of any substance used as a nutritive substance permitted by the Standard to be declared in the NIS. The substances 2'-FL/DFL, LNT, 6'-SL and 3'-SL would need to be declared in the NIS when they are voluntarily added to an IFP.

2.2.8.3 Prohibited representations

Paragraph 2.9.1—24(1)(ca) prohibits the use of the words 'human milk oligosaccharide', 'human milk identical oligosaccharide' or any word or words having the same or similar effect. In addition, paragraph 2.9.1—24(1)(cb) prohibits the use of the abbreviations 'HMO' or 'HiMO' or any abbreviation having the same or similar effect. The words and abbreviations in these provisions cannot be used anywhere on the label of a package of IFP. The substances 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt would be subject to these provisions regarding prohibited representations.

2.2.8.4 Voluntary representations

Paragraph 1.2.7—4(b) states that a nutrition content or health claim must not be made about an IFP. Paragraph 2.9.1—24(1)(f) also prohibits a reference to the presence of a nutrient or substance that may be used as a nutritive substance, except for a reference in: a statement relating to lactose under subsection 2.9.1—14(6), a statement of ingredients, or in the NIS. These existing prohibitions for nutrition content and health claims for IFP would apply to the substances 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt.

2.2.8.5 Labelling as 'genetically modified'

As discussed in section 2.3 of SD1, the substances 2'-FL/DFL, LNT, 6'-SL and 3'-SL 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 or novel DNA will be present in an IFP that contains these substances as ingredients. However, where novel protein or novel DNA is present, the requirement to label 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as 'genetically modified' would apply in accordance with section 1.5.2—4.

2.2.9 Exclusivity

An applicant may request exclusive permission to use and sell a nutritive substance for a

period of up to 15 months to recognise the investment made in developing that nutritive substance and the need to achieve return on this investment, thereby supporting innovation.

The Applicant has requested an exclusive use permission for their specific brand of 2'-FL/DFL, LNT, 6'-SL and 3'-SL, alone or in combination in IFP, on the basis that there has been significant research and investment by the Applicant into the development of these highly refined products obtained via proprietary manufacturing processes.

FSANZ is proposing to provide the Applicant with a 15 month exclusive use permission for the permitted forms of 2'-FL/DFL, LNT, 6'-SL and 3'-SL, commencing on the date of gazettal of the draft variation (if approved).

If the draft variation is approved, this means that, during that 15 month period, the permission would apply exclusively to those substances under the brand names “GlyCare™ 2FL/DFL 8001, GlyCare™ LNT 8001, GlyCare™ 6SL 9001, and GlyCare™ 3SL 9001” in accordance with the Code.

Once the 15 month period ends, the exclusive use permission would revert to a general permission, meaning that anyone may use the permitted forms of 2'-FL/DFL, LNT, 6'-SL and 3'-SL in accordance with the Code.

An exclusive use 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.

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

FSANZ is committed to reviewing any new evidence on the beneficial role of HiMOs in the normal growth and development of infants.

At the request of Food Ministers, FSANZ will carry out a five-year review (to be completed by March 2026) of the initial permission gazetted under Application A1155. This will review the evidence of a substantiated beneficial role of 2′-FL and LNnT in the normal growth and development of infants. This process will include consultation with a range of stakeholders including experts, industry and government agencies, and will be independently peer reviewed.

FSANZ has started the review by defining the research questions, reviewing existing evidence and seeking out the relevant data needed, including from industry and recently published studies. Details on the review process, including stakeholder input will be made available on the FSANZ website.

2.2.11 Risk Management conclusion

FSANZ has considered the maximum amounts requested for 2'-FL/DFL, LNT, 6'-SL and 3'-SL in the context of the safety, technical, nutrition and health effects assessment. This included estimated dietary intakes and naturally occurring levels in human milk, potential beneficial health effects and alignment with international regulations. Based on this assessment which found no public health and safety concerns with the requested permissions, FSANZ has prepared a draft variation to the Code to permit the voluntary addition of 2'-FL/DFL, LNT, 6'-SL and 3'-SL, meeting the Applicant’s specifications, to IFP.

The proposed approach to permit these substances individually supports the principle of minimum effective regulation and minimisation of technical barriers to trade.

If the draft variation is approved, the addition of the permitted forms of 2'-FL/DFL, LNT, 6'-SL and 3'-SL to IFP will be subject to relevant requirements and conditions in the Code, which include the following:

- The existing prohibition for the use of the words 'human milk identical oligosaccharide' or 'human milk oligosaccharide', and abbreviations 'HMO', 'HiMO' or any word or words or abbreviations having the same or similar effect, will apply to IFP that contain 2'-FL/DFL, LNT, 6'-SL and 3'-SL covered by the variation.
- An exclusive permission to use of 2'-FL/DFL, LNT, 6'-SL and 3'-SL produced by microbial fermentation using a GM strain of *E. coli* K-12 will apply for a period of 15 months, under the Applicant's brand name GlyCare™ (covering Applicant's products GlyCare™ 2FL/DFL 8001, GlyCare™ LNT 8001, GlyCare™ 6SL 9001, and GlyCare™ 3SL 9001), commencing on the date of gazettal of the approved draft variation.
- Schedule 3 of the Code will set new specifications for 2'-FL/DFL, LNT, 6'-SL and 3'-SL using the specifications proposed by the Applicant.

The draft variation reflecting this option is at Attachment A. The draft explanatory statement for the variation is in Attachment B.

2.3 Risk communication

2.3.1 Consultation

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

FSANZ developed and applied a standard communication strategy to this Application. All calls for submissions are notified via the FSANZ Notification Circular, media release, through FSANZ's social media channels and Food Standards News.

Subscribers and interested parties are also notified about the availability of reports for public comment. The draft variation will be considered for approval by the FSANZ Board taking into account all public comments received on this call for submissions.

The Applicant and individuals and organisations that make submissions on this Application will be notified at each stage of the assessment.

2.3.2 World Trade Organization (WTO)

As members of the World Trade Organization (WTO), Australia and New Zealand are obliged to notify WTO members where proposed mandatory regulatory measures are inconsistent with any existing or imminent international standards and the proposed measure may have a significant effect on trade.

There are relevant international standards and amending the Code to permit the voluntary addition of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL, alone or in combination, is unlikely to have a significant effect on international trade as the individual ingredients are permitted in similar products without prohibition of the combination, or the combination is expressly permitted in some countries overseas. Therefore, a notification to the WTO under

Australia's and New Zealand's obligations under the WTO Technical Barriers to Trade or Application of Sanitary and Phytosanitary Measures Agreement was not considered necessary.

2.4 FSANZ Act assessment requirements

When assessing this Application and the subsequent development of a food regulatory measure, 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

As explained above, Application A1265 seeks an amendment of the Code to allow the addition of the Applicant's 2'-FL/DFL, LNT, 6'-SL and 3'-SL, alone or in combination, to infant formula products (IFP).

The Office of Impact Analysis (OIA) has granted FSANZ a standing exemption from the requirement to develop a Regulatory Impact Statement (RIS) for permitting genetically modified foods (OIA correspondence dated 24 November 2010, reference 12065) and for the voluntary addition of nutritive substances to foods (OIA correspondence dated 16 April 2013, reference 14943).

FSANZ however considered the costs and benefits that could arise from the proposed measure for the purposes of meeting FSANZ Act considerations. The FSANZ Act requires FSANZ to have regard to whether the direct and indirect benefits that would arise from a food regulatory measure developed or varied as a result of the Application would outweigh the costs to the community, government or industry that would arise from the development or variation of that food regulatory measure.

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 (where the status quo is rejecting the Application).

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 potential positives and negatives of moving away from the status quo by approving this Application.

Consumers

Consumers may benefit from improved health outcomes. The link between 2'-FL/DFL, LNT, 6'-SL and 3'-SL, alone or in combination, and improved health outcomes for infants is discussed earlier in this document.

Caregiver understanding and behaviour is not expected to be significantly impacted. A literature review of studies between 2003 and 2019 undertaken by FSANZ to inform Proposal P1028 highlighted that caregivers often lack knowledge about the contents of ingredient lists and nutritional information statements, particularly what different nutrients are and the benefits they have. Many caregivers report not reading the ingredients list, often because they do not understand what the ingredients are (FSANZ 2022b).

On balance, FSANZ considers it unlikely that a significant proportion of consumers will notice the additional ingredients and alter their purchasing behaviour as a result.

Industry

Industry may benefit from increased choice of ingredients for domestically sold and imported IFP. Industry will voluntarily use alone or in combination 2'-FL/DFL, LNT, 6'-SL and 3'-SL or buy and sell IFP containing either, where a commercial benefit exists for them.

Given addition of 2'-FL/DFL, LNT, 6'-SL and 3'-SL in IFP is already approved in some overseas countries (see Section 1.4), granting the permission requested by the Application would favour trade and any growth of overseas markets for domestic IFP exporters. Approving the requested permission may also promote and support innovation in IFP.

Greater industry competition is generally assumed to lead to IFP producers competing more on variety and price of IFP, leading to consumers accessing a higher variety and/or lower prices of IFP. If producer A sells a similar product to producer B at a lower price, consumers would likely buy from producer A to save money. Consumers would also likely buy from producer A if their product were the same price as producer B's but is a more appealing variety.

The proposed exclusivity period creates an incentive to innovate, however the extent of the incentive is limited by the time limit.

Government

The approval of this Application may result in a small but likely inconsequential cost to government from an additional combination of IFP ingredients that is monitored for compliance with individual ingredient maximum limits. That assumes an increase in IFP containing 2'-FL/DFL, LNT, 6'-SL and 3'-SL.

Conclusion

FSANZ's current assessment is that the direct and indirect benefits that would arise from approving this Application most likely outweigh the associated costs.

However information received from this call for submissions, may result in FSANZ arriving at a different conclusion.

2.4.1.2 Other measures

There are no other measures (whether available to FSANZ or not) that would be more cost-effective than a food regulatory measure developed or varied as a result of the Application.

2.4.1.3 Any relevant New Zealand standards

The relevant standards apply in both Australia and New Zealand. There are no relevant New Zealand only 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 completed a safety and risk assessment (Supporting Document 1) which is summarised in Section 2.1 of this Report. The assessment concluded that there are no public health and safety concerns from the addition of 2′-FL/DFL, LNT, 6′-SL or 3′-SL at the proposed amounts. Additionally, the weight of evidence supports beneficial health effects of HiMOs added to IFP.

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

Current labelling requirements discussed in section 2.2.8 would apply to 2'-FL/DFL, LNT, 6'-SL, and 3'-SL when added to IFP and would provide information to enable consumers to make an informed choice.

2.4.2.3 The prevention of misleading or deceptive conduct

Current labelling requirements, including prohibited representations which aim to prevent misleading or deceptive conduct, would apply to IFP containing 2'-FL/DFL, LNT, 6'-SL, and 3'-SL, either individually or in combination (see Section 2.2.8.3 above).

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**

Using risk analysis, FSANZ considered the best available evidence to reach its conclusions on the safety, technical, nutrition and beneficial health effects of the addition of 2'-FL/DFL, LNT, 6'-SL, and 3'-SL in IFP.

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

FSANZ considered the promotion of consistency between domestic and international food standards and the desirability of an efficient and internationally competitive food industry. HiMOs including those requested in this Application are permitted for addition to equivalent IFP in other overseas jurisdictions. The permission will promote consistency between domestic and a number of international food standards. See also Section 1.4 of this Report.

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

The proposed permissions would support an internationally competitive food industry in relation to the addition of 2'-FL/DFL, LNT, 6'-SL, and 3'-SL to IFP.

Additionally, removing the existing prohibition for the use of ITF and/or GOS with LNnT in IFP and not applying the prohibition to 2'-FL/DFL, LNT, 6'-SL, and 3'-SL aligns with the Code

permissions for 2′-FL as an individual ingredient and will support an internationally competitive food industry.

- **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**

FSANZ has had regard to both high order and specific policy principles in relevant Ministerial Policy Guidelines. Two Ministerial Policy Guidelines specifically applied to this Application:

  - Regulation of Infant Formula Products
  - Intent of Part 2.9 of the Food Standards Code –Special Purpose Foods.

Noting the food technology aspects, safety, nutritional impact and beneficial health effects assessed in SD1 and Section 2.2.2 of this Report, FSANZ considers these Policy Guidelines have been met.

3 Draft variation

The draft variation to the Code is at Attachment A and is intended to take effect on gazettal.

A draft explanatory statement is at Attachment B. An explanatory statement is required to accompany an instrument if it is lodged on the Federal Register of Legislation.

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Appendix: Calculation of cumulative oligosaccharide amounts

The table below was reproduced from EC SCF (2003) which reported the calculated carbohydrate content of infant formula based on protein and fat content.

Macronutrient amounts in Standard 2.9.1 - as proposed in Proposal P1028 2nd Call for Submissions (CFS)*:*

	Minimum	**Maximum**
Energy	2510 kJ/L	2930 kJ/L
Protein	0.43 g/100 kJ	0.72 g/100 kJ
Fat	1.1 g/100 kJ	1.4 g/100 kJ
CHO	By difference	By difference

Protein and fat amounts (minimum and maximum) are calculated as a percentage of the energy density (at maximum and minimum permitted energy) based on Atwater factors[14]: 1 g fat = 37 kJ, 1 g carbohydrate (CHO) = 17 kJ, 1 g protein = 17 kJ.

For each minimum and maximum, total carbohydrate expressed as percentage of energy density was derived from 100 – (%Energy $_{fat}$ + %Energy $_{protein}$).

In Table 1 (Section 2.2.5), the oligosaccharide content calculated as a percentage of energy density was based on the Atwater factor for unavailable carbohydrate[1] (1 g carbohydrate = 8 kJ). This was calculated to be 1.2% for the combined HiMO permissions only, and 4.4% if ITF and GOS are included.

Macronutrient	**At Energy Minimum = 2510 kJ/L**				**At Energy Maximum = 2930 kJ/L**			
Fat	Minimum		Maximum		Minimum		Maximum	
g/100 kJ	1.1		1.4		1.1		1.4	
%Energy	40.7		51.8		40.7		51.8	
Protein	Min	Max	Min	Max	Min	Max	Min	Max
g/100 kJ	0.43	0.72	0.43	0.72	0.43	0.72	0.43	0.72
% Energy	7.3	12.2	7.3	12.2	7.3	12.2	7.3	12.2
%Energy$_{F+P}$	48	53	59	64	48	53	59	64
%Energy CHO$_{total}$	52	47	41	36	52	47	41	36
CHO$_{total}$ *g/100 kJ*	3.1	2.8	2.4	2.1	3.1	2.8	2.4	2.1

[14] FAO (2003) Food and Nutrition Paper 77: Food energy - methods of analysis and conversion factors. Report of a Technical Workshop, Rome. ISBN 92-5-105014-7

Attachments

A. Draft variation to the Australia New Zealand Food Standards Code
B. Draft Explanatory Statement

Attachment A – Approved draft variation to the *Australia New Zealand Food Standards Code*

Food Standards (Application A1265 – 2'FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation

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The Board of Food Standards Australia New Zealand gives notice of the making of this variation under section 92 of the *Food Standards Australia New Zealand Act 1991*. The variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by the Delegate]

[Insert Delegate's name and position title]
Delegate of the Board of Food Standards Australia New Zealand

Note:

This variation will be published in the Commonwealth of Australia Gazette No. FSC XX on XX Month 20XX. This means that this date is the gazettal date for the purposes of clause 3 of the variation.

1 Name

This instrument is the *Food Standards (Application A1265 –2′-FL/DFL, LNT, 6′-SL sodium salt and 3′-SL sodium salt as nutritive substances in infant formula products) Variation*.

2 Variation to standards in the *Australia New Zealand Food Standards Code*

The Schedule varies Standards in the *Australia New Zealand Food Standards Code*.

3 Commencement

The variation commences on the date of gazettal.

Schedule

Standard 2.9.1—Infant formula products

[1] Subsection 2.9.1—7(2)

Repeal the subsection.

Schedule 3—Identity and purity

[2] Subsection S3—2(2)(table)

Insert:

2′-fucosyllactose and difucosyllactose sourced from *Escherichia coli K-12*	section S3—47
lacto-N-tetraose sourced from *Escherichia coli K-12*	section S3—48
6′-sialyllactose sodium salt sourced from *Escherichia coli K-12*	section S3—49
3′-sialyllactose sodium salt sourced from *Escherichia coli K-12*	section S3—50

[3] After section S3—46

Insert:

S3—47 Specification for a combination of 2′-fucosyllactose and difucosyllactose sourced from *Escherichia coli K-12*

For a mixture of 2′-fucosyllactose (2′-FL) and difucosyllactose (DFL) sourced from *Escherichia coli K-12* containing the gene for alpha-1,2-fucosyltransferase from *Helicobacter pylori*, the specifications are the following:

(a) chemical names:
  (i) for 2′-FL—α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-D-glucopyranose;
  (ii) for DFL—α-L-fucopyranosyl-(1→2)-β-D-galactopyranosyl-(1→4)-[α-L-fucopyranosyl-(1→3)]-D-glucose;

(b) chemical formulas:
  (i) for 2′-FL—$C_{18}H_{32}O_{15}$;
  (ii) for DFL—$C_{24}H_{42}O_{19}$;

(c) molecular weights:
  (i) for 2′-FL—488.44 g/mol;
  (ii) for DFL—634.58 g/mol;

(d) CAS numbers:

(i) for 2′-FL—41263-94-9;

(ii) for DFL—20768-11-0;

(e) description—white, white to off-white, or off-white powder, agglomerates, or powder with agglomerates;

(f) 2′-FL—not less than 75.0%;

(g) DFL—not less than 5.0%;

(h) sum of 2′-FL and DFL—not less than 85.0%;

(i) sum of human identical milk saccharides: 2′-FL, DFL, D-lactose, L-fucose, 3-fucosyllactose FL—Not less than 92.0%;

(j) D-lactose—not more than 10%;

(k) L-fucose—not more than 1.0%;

(l) 2'-fucosyl-D-lactulose—not more than 2.0%;

(m) pH (20°C, 5% solution)—4.0-6.0;

(n) water—not more than 6.0%;

(o) ash, sulphated—not more than 0.8%;

(p) residual protein—not more than 0.01%;

(q) lead—not more than 0.1 mg/kg;

(r) microbiological:

(i) aerobic mesophilic bacteria total count—not more than 1,000 cfu/g;

(ii) *Enterobacteriaceae*—absent in 10 g;

(iii) yeasts—not more than 100 cfu/g;

(iv) moulds—not more than 100 cfu/g;

(v) residual endotoxins—not more than 10 EU/mg.

S3—48 Specification for lacto-N-tetraose sourced from *Escherichia coli K-12*

For lacto-N-tetraose (LNT) sourced from *Escherichia coli K-12* containing the gene for beta-1,3-N-acetylglucosaminyltransferase from *Neisseria meningitides* and the gene for beta-1.3-galactosyltransferase from *Helicobacter pylori*, the specifications are the following:

(a) chemical name—β-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→4)-D-glucose;

(b) chemical formula—$C_{26}H_{45}NO_{21}$;

(c) molecular weight—707.63 g/mol;

(d) CAS number—14116-68-8;

(e) description—white, white to off-white, or off-white powder, agglomerates, or powder with agglomerates;

(f) LNT—not less than 70.0%;

(g) sum of human identical milk saccharides: LNT, D-lactose, lacto-N-triose II—not less than 90.0%;

(h) D-lactose—not more than 12.0%;

(i) lacto-N-triose II—not more than 10.0%

(j) *para*-lacto-N-hexaose—not more than 3.5%;

(k) β-D-Galactopyranosyl-(1→3)-2-acetamido-2-deoxy-β-D-glucopyranosyl-(1→3)-β-D-galactopyranosyl-(1→4)-D-fructose (LNT fructose isomer)—not more than 1.0%;

(l) pH (20°C, 5% solution)—4.0-6.0;

(m) water—not more than 6.0%;

(n) residual protein—not more than 0.01%;

(o) ash, sulphated—not more than 0.5%;

(p) lead—not more than 0.1 mg/kg;

(q) microbiological:

(i) aerobic mesophilic bacteria total count—Not more than 1,000 cfu/g;

(ii) *Enterobacteriaceae*—absent in 10 g;

(iii) yeasts—not more than 100 cfu/g;

(iv) moulds—not more than 100 cfu/g;

(v) residual endotoxins—not more than 10 EU/mg.

S3—49 Specification for 6′-sialyllactose sodium salt sourced from *Escherichia coli K-12*

For 6′-sialyllactose sodium salt (6′-SL) sourced from *Escherichia coli K-12* containing the gene for alpha-2,6-sialyltransferase from *Photobacterium damsela* and CMP-Neu5Ac synthetase, Neu5Ac synthetase, *N*-acetylglucosamine-6-phosphatase epimerase from *Campylobacter jejuni*, the specifications are the following:

(a) chemical name—N-acetyl-α-D-neuraminyl-(2→6)-β-D-galactopyranosyl-(1→4)-D-glucose, sodium salt;

(b) chemical formula—$C_{23}H_{38}NO_{19}Na$;

(c) molecular weight—655.53 g/mol;

(d) CAS number—157574-76-0;

(e) description—white, white to off-white, or off-white powder, agglomerates, or powder with agglomerates;

(f) 6′-SL—not less than 90.0%;

(g) sum of human identical milk saccharides: 6′-SL sodium salt, D-lactose, sialic acid—not less than 94.0%;

(h) D-lactose—not more than 5.0%;

(i) sialic acid—not more than 2.0%;

(j) sialyl-lactulose—6’- isomer—not more than 3.0%;

(k) sodium—2.5-4.5%;

(l) chloride—not more than 1.0%;

(m) pH (20°C, 5% solution)—4.5-6.0;

(n) water—not more than 6.0%;

(o) residual protein—not more than 0.01%;

(p) lead—not more than 0.1 mg/kg;

(q) microbiological:

(i) aerobic mesophilic total plate count—not more than 1,000 cfu/g;

(ii) *Enterobacteriaceae*—absent in 10 g;

(iii) yeasts—not more than 100 cfu/g;

(iv) moulds—not more than 100 cfu/g;

(v) residual endotoxins—not more than 10 EU/mg.

S3—50 Specification for 3′-sialyllactose sodium salt sourced from *Escherichia coli K-12*

For 3′-sialyllactose sodium salt (3′-SL) sourced from *Escherichia coli K-12* containing the gene for alpha-2,3-sialyltransferase from *Neisseria meningitides* and CMP-Neu5Ac synthetase, Neu5ac synthase, *N*-acetylglucosamine-6-phosphatase epimerase from *Campylobacter jejuni*, the specifications are the following:

(a) chemical name—N-acetyl-α-D-neuraminyl-(2→3)-β-D-galactopyranosyl-(1→4)-D-glucose, sodium salt;

(b) chemical formula—$C_{23}H_{38}NO_{19}Na$;

(c) molecular weight—655.53 g/mol;

(d) CAS number—128596-80-5;

(e) description—white, white to off-white, or off-white powder, agglomerates, or powder with agglomerates;

(f) 3′-SL—not less than 88.0%;

(g) sum of human identical milk saccharides: 3′-SL sodium salt, D-lactose, sialic acid—not less than 90.0%;

(h) D-lactose—not more than 5.0%;

(i) sialic acid—not more than 1.5%;

(j) sialyl-lactulose-3′-isomer—not more than 5.0%;

(k) sodium—2.5-4.5%;

(l) chloride—not more than 1.0%;

(m) pH (20°C, 5% solution)—4.5-6.0;

(n) water—not more than 8.0%;

(o) residual protein—not more than 0.01%;

(p) lead—not more than 0.1 mg/kg;

(q) microbiological:

(i) aerobic mesophilic total plate count—not more than 1,000 cfu/g;

(ii) *Enterobacteriaceae*—absent in 10 g;

(iii) yeasts—not more than 100 cfu/g;

(iv) moulds—not more than 100 cfu/g;

(v) residual endotoxins—not more than 10 EU/mg.

Schedule 26—Food produced using gene technology

[4] Subsection S26—3(7) (table)

Insert:

4	**A combination of 2′-fucosyllactose and difucosyllactose**	*Escherichia coli* K-12 containing the gene for alpha-1,2-fucosyltransferase from *Helicobacter pylori*	1. May only be added to infant formula products. 2. During the exclusive use period, may only be sold under the brand GlyCare 2′-FL/DFL 8001. 3. For the purposes of condition 2 above, **exclusive use period** means the period commencing on the date of gazettal of the *Food Standards (Application A1265 – 2′-FL/DFL, LNT, 6′-SL sodium salt and 3′-SL sodium salt as nutritive substances in infant formula products) Variation* and ending 15 months after that date.

5	**lacto-N-tetraose**	*Escherichia coli* K-12 containing the gene for beta-1,3- N-acetylglucosaminyltransferase from *Neisseria meningitides* and the gene for beta-1,3-galactosyltransferase from *Helicobacter pylori*	1. May only be added to infant formula products. 2. During the exclusive use period, may only be sold under the brand GlyCare LNT8001. 3. For the purposes of condition 2 above, **exclusive use period** means the period commencing on the date of gazettal of the *Food Standards (Application A1265 – 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation* and ending 15 months after that date.
6	**6′-sialyllactose sodium salt**	*Escherichia coli* K-12 containing the gene for alpha-2,6-sialyltransferase from *Photobacterium damsela* and CMP-Neu5Ac synthetase, Neu5Ac synthase, N-acetylglucosamine-6-phosphatase epimerase from *Campylobacter jejuni*	1. May only be added to infant formula products. 2. During the exclusive use period, may only be sold under the brand GlyCare 6SL 9001. 3. For the purposes of condition 2 above, **exclusive use period** means the period commencing on the date of gazettal of the *Food Standards (Application A1265 – 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation* and ending 15 months after that date.
7	**3′-sialyllactose sodium salt**	*Escherichia coli* K-12 containing the gene for alpha-2,3-sialyltransferase from *Neisseria meningitides* and CMP-Neu5Ac synthetase, Neu5Ac synthase, N-acetylglucosamine-6-phosphatase epimerase from *Campylobacter jejuni*	1. May only be added to infant formula products. 2. During the exclusive use period, may only be sold under the brand GlyCare 3SL 9001. 3. For the purposes of condition 2 above, **exclusive use period** means the period commencing on the date of gazettal of the *Food Standards (Application A1265 – 2'-FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation* and ending 15 months after that date.

Schedule 29—Special purpose foods

[5] Section S29—5 (table)

Insert each of the following substances in alphabetical order:

3'-sialyllactose sodium salt permitted for use by Standard 1.5.2	3'-sialyllactose sodium salt	8 mg
6'-sialyllactose sodium salt permitted for use by Standard 1.5.2	6'-sialyllactose sodium salt	16 mg
A combination of 2′-fucosyllactose and difucosyllactose, permitted for use by Standard 1.5.2	2'-fucosyllactose and difucosyllactose	96 mg
lacto-N-tetraose permitted for use by Standard 1.5.2	lacto-N-tetraose	32 mg

Attachment B

EXPLANATORY STATEMENT

Food Standards Australia New Zealand Act 1991

Food Standards (Application A1265 – 2'FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation

1. Authority

Section 13 of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act) provides that the functions of Food Standards Australia New Zealand (the Authority) include the development of standards and variations of standards for inclusion in the *Australia New Zealand Food Standards Code* (the Code).

Division 1 of Part 3 of the FSANZ Act specifies that the Authority may accept applications for the development or variation of food regulatory measures, including standards. This Division also stipulates the procedure for considering an application for the development or variation of food regulatory measures.

The Authority accepted Application A1265 which sought to permit the use of four human-identical milk oligosaccharide products, each derived from a specific genetically modified *Escherichia coli* (*E.coli*) strain, as nutritive substances in infant formula products. The four products or substances are:

- a mixture of 2'-fucosyllactose (2'-FL) and difucosyllactose (DFL) (2'-FL/DFL);
- lacto-N-tetraose (LNT);
- 6'-sialyllactose sodium salt (6'-SL); and
- 3'-sialyllactose sodium salt (3'-SL).

The Application also sought a 15 month exclusive use permission.

The Authority assessed the Application in accordance with Division 1 of Part 3 of the FSANZ Act. During that assessment, the Authority identified a need to amend the Code to remove the current prohibition on the addition to infant formula products of galacto-oligosaccharides and/or inulin-type fructans in combination with lacto-N-neotetraose (LNT). Removal of this prohibition was not requested in Application A1265, but was considered warranted by the Authority. Based on that assessment, the Authority prepared a draft variation - the *Food Standards (Application A1265 – 2'FL/DFL, LNT, 6'-SL sodium salt and 3'-SL sodium salt as nutritive substances in infant formula products) Variation*.

2. Variation will be a legislative instrument

If approved, the draft variation would be a legislative instrument for the purposes of the *Legislation Act 2003* (see section 94 of the FSANZ Act) and be publicly available on the Federal Register of Legislation (www.legislation.gov.au).

If approved, this instrument would not be subject to the disallowance or sunsetting provisions of the *Legislation Act 2003.* Subsections 44(1) and 54(1) of that Act provide that a legislative instrument is not disallowable or subject to sunsetting if the enabling legislation for the instrument (in this case, the FSANZ Act): (a) facilitates the establishment or operation of an intergovernmental scheme involving the Commonwealth and one or more States; and (b) authorises the instrument to be made for the purposes of the scheme. Regulation 11 of the

Legislation (Exemptions and other Matters) Regulation 2015 also exempts from sunsetting legislative instruments a primary purpose of which is to give effect to an international obligation of Australia.

The FSANZ Act gives effect to an intergovernmental agreement (the Food Regulation Agreement) and facilitates the establishment or operation of an intergovernmental scheme (national uniform food regulation). That Act also gives effect to Australia's obligations under an international agreement between Australia and New Zealand. For these purposes, the Act establishes the Authority to develop food standards for consideration and endorsement by the Food Ministers Meeting (FMM). The FMM is established under the Food Regulation Agreement and the international agreement between Australia and New Zealand, and consists of New Zealand, Commonwealth and State/Territory members. If endorsed by the FMM, the food standards on gazettal and registration are incorporated into and become part of Commonwealth, State and Territory and New Zealand food laws. These standards or instruments are then administered, applied and enforced by these jurisdictions' regulators as part of those food laws.

3. Purpose

The purpose of the draft variation prepared by the Authority is to:

- amend Schedule 29 of the Code to permit each of the four substances to be used in infant formula products, either alone or in combination, as a nutritive substance up to a specified maximum permitted amount;
- amend Schedule 26 of the Code to permit each of the four substances, as substances derived from a new genetically modified microbial source, to be added to infant formula products subject to certain conditions, including an exclusive use period of 15 months for the applicant's brand of each substance;
- amend Schedule 3 of the Code to include identity and purity specifications for each of the four substances; and
- remove the current prohibition in Standard 2.9.1 on the use of galacto-oligosaccharides and/or inulin-type fructans with lacto-N-neotetraose.

4. Documents incorporated by reference

The draft variation prepared by the Authority does not incorporate any documents by reference.

However, the approved draft variation will vary Schedule 3 of the Code which does incorporate documents by reference. Section 1.1.1—15 of the Code requires certain substances (such as substances used as nutritive substances) to comply with any relevant identity and purity specifications listed in Schedule 3.

Schedule 3 incorporates documents by reference to set specifications for various substances in the circumstances specified in that Schedule. The documents incorporated include: the Joint FAO/WHO Expert Committee on Food Additives (JECFA) Compendium of Food Additive Specifications (FAO/WHO 2019); the United States Pharmacopeial Convention (2020) Food Chemicals Codex (12th edition); and the Commission Regulation (EU) No 231/2012.

5. Consultation

In accordance with the procedure in Division 1 of Part 3 of the FSANZ Act, the Authority's consideration of Application A1265 will include one round of public consultation following an assessment and the preparation of a draft variation and associated assessment summary. A

call for submissions (including the draft Standard/variation) will be open for a 4 week period.

A Regulation Impact Statement was not required because the Office of Best Practice Regulation (OBPR) granted FSANZ a standing exemption, permitting the voluntary use of genetically modified food (OBPR correspondence dated 24 November 2010, reference 12065), and the voluntary addition of nutritive substances to foods (OBPR correspondence dated 16 April 2013, reference 14943). This standing exemption was provided as permitting genetically modified food and nutritive substances is deregulatory as their use will be voluntary if the application concerned is approved. This standing exemption relates to the introduction of a food to the food supply that has been determined to be safe.

6. Statement of compatibility with human rights

If approved, this instrument would be exempt from the requirements for a statement of compatibility with human rights as it is a non-disallowable instrument under section 44 of the Legislation Act 2003.

7. Variation

Item [1] of the Schedule will amend Standard 2.9.1 by repealing subsection 2.9.1—7(2). The effect of this amendment will be to remove the current prohibition on the addition to infant formula products of galacto-oligosaccharides and/or inulin-type fructans in combination with lacto-N-neotetraose.

Items [2] and [3] of the Schedule will amend Schedule 3 of the Code.

Schedule 3 contains specifications for the purposes of section 1.1.1—15 of the Code. Section 1.1.1—15 requires certain substances, e.g. substances used as nutritive substances, to comply with any relevant identity and purity specifications listed in Schedule 3. Specifications include those set out in provisions which are listed in the table to subsection S3—2(2) (see paragraph S3—2(1)(a)).

The amendments made by Items [2] and [3] will set – for the purposes of section 1.1.1—15 of the Code - a specifications for each of the four substances listed above.

Item [2] will amend the table to subsection S3—2(2) by inserting in alphabetical order new entries for

- ‘2′-fucosyllactose and difucosyllactose sourced from *Escherichia coli K-12’* and a corresponding reference to new section S3—47 (see item [3] below)
- ‘lacto-N-tetraose sourced from *Escherichia coli K-12’* and a corresponding reference to new section S3—48 (see item [3] below)
- ‘6′-sialyllactose sodium salt sourced from *Escherichia coli K-12’* and a corresponding reference to new section S3—49 (see item [3] below)
- ‘3′-sialyllactose sodium salt sourced from *Escherichia coli K-12’* and a corresponding reference to new section S3—50 (see item [3] below)

Item [3] will insert new sections S3—47, S3—48, S3—49 and S3—50 into Schedule 3 in numerical order after S3—46.

New section S3—47 will list a specification for 2′-fucosyllactose and difucosyllactose sourced from *Escherichia coli K-12.*

New section S3—48 will list a specification for lacto-N-tetraose sourced from *Escherichia coli K-12.*

New section S3—49 will list a specification for 6′-sialyllactose sodium salt sourced from *Escherichia coli K-12.*

New section S3—50 will list a specification for 3′-salyllactose sodium salt sourced from *Escherichia coli K-12.*

Item [4] of the Schedule will amend Schedule 26 of the Code.

Schedule 26 relates to food produced using gene technology. Each of the four substances listed above is a food produced using gene technology (as defined in subsection 1.1.2—2(3) of the Code) because it is derived from an organism modified using gene technology. That is, from a genetically modified *Escherichia coli* (*E.coli*) K-12 strain.

Paragraph 1.5.2—3(a) permits a food for sale to consist of, or have as an ingredient, a food produced using gene technology if the food produced using gene technology (other than a processing aid or food additive) is listed in Schedule 26 and complies with any corresponding conditions in that Schedule.

The table to subsection S26—3(7) lists food produced using gene technology of microbial origin. Item [4] will amend that table by adding new table items 4 to 7 to provide a permission for the use of each of the four substances.

Each permission will be subject to conditions of use set out in column 3. These conditions of use are as follows:

1. the substance may only be added to infant formula products;
2. during the exclusive use period, the substance may only be sold under the brand name specified by and for that permission; and
3. for the purposes of condition 2, exclusive use period means the period commencing on the date of gazettal of the draft variation and ending 15 months after that date.

Condition 2 will mean that each substance, as a permitted food produced using gene technology, may only be sold under the specified brand during the exclusive use period. ‘Exclusive use period’ will be defined in condition 3 as the period commencing upon gazettal of the draft variation and ending 15 months after that date

Once this period ends, each permission will revert to a general permission, meaning that the proposed permission will then permit the four substances sourced from the specified genetically modified *Escherichia coli* (*E.coli*) strain to be sold under any brand.

The proposed amendments made by item [4] will not make any substantive change to *existing* permissions and to other requirements in the Code relating to food produced using gene technology.

Item [5] of the Schedule will amend Schedule 29 of the Code.

The item will amend the table to section S29—5. The table lists the new substances permitted for use as nutritive substances in infant formula products. The item will amend the table by inserting into that table in alphabetical order a separate new permission for each of the following:

- 3'-sialyllactose sodium salt, with a specified maximum permitted amount of 8 mg/100 kJ;
- 6'-sialyllactose sodium salt, with a specified maximum permitted amount of 16 mg/100 kJ;
- a combination of 2'-fucosyllactose and difucosyllactose, with a specified maximum permitted amount of 96 mg/100 kJ; and

- lacto-N-tetraose, , with a specified maximum permitted amount of 32 mg/100 kJ.

A minimum amount is not set for each permission or substance as this was not requested in the Application and has not been determined by the Authority.

Each permission will prescribe a permitted form for the permitted substance. This will mean that the substance must be used in that form.

Each permission is also expressly linked to these substances as permitted for use by Standard 1.5.2 (*Food produced using gene technology*). This means that only those substances derived from the relevant microbial source listed in Schedule 26 (table to subsection 26—3(7)) for that substance will be permitted for use as a nutritive substance in infant formula products.