Comments from the Victorian Department of Health and Human Services and the Victorian Department of Jobs, Precincts and Regions.

Due date of submission – 17 January 2019

The Victorian Departments of Health and Human Services and Jobs, Precincts and Regions (the departments) welcome the opportunity to respond to this application to amend the Australia New Zealand Food Standards Code (the Code).

Application A1155 – 2'-FL and LNnT in infant formula and other products (the Application) seeks to permit the voluntary addition of 2'-O-Fucosyllactose (2'-FL), either alone or in combination with Lacto-N-neotetraose (LNnT) to infant formula and formulated supplementary foods for young children (FSFYC), also known as toddler milk. The Application has been submitted by Glycom A/S (the Applicant).

From the Food Standards Australia New Zealand (FSANZ) Assessment report and supporting documents, it is understood that:

- 2'-FL and LNnT are oligosaccharides found naturally in human milk.
- The Application is seeking permission to add human milk identical 2'-FL and LNnT, produced by microbial fermentation from genetically modified strains of *Escherichia coli* (*E.coli*) SCR6 and *E.coli* MP572 to infant formula and FSFYC.
- FSANZ proposes to permit a maximum level higher than the level requested by the Applicant. The proposed higher permitted level is a maximum of 96mg/100kJ of 2'-FL when added alone, or 24mg/kJ of LNnT and a combined maximum of 96mg/100kJ of LNnT and 2'-FL when both are added in combination in infant formula. This is equivalent to a maximum of 2.4g/L of 2'-FL alone, and 2.4g/L of 2'-FL and LNnT combined, with no more than 0.6g/L of LNnT.
- For consistency in the Code, FSANZ proposes to permit the same maximum levels in FSFYC, but to require these levels to be expressed per serving unit.
- Further, FSANZ intends to prohibit the addition of 2'-FL alone, or with LNnT, in combination with existing permissions for galacto-oligosaccharides (GOS) and inulin-type fructans (ITF).
- FSANZ concluded that there were no public health or safety concerns associated with the addition of 2'-FL alone or in addition to LNnT at either the levels proposed by the Applicant or those proposed by FSANZ. This conclusion was based on information on the absorption, distribution, metabolism and excretion, as well as toxicity studies, human clinical studies in infants and adults (noting that the levels studied in infants were lower than the level proposed by FSANZ), and the fact that the proposed levels are consistent with those found naturally in human milk.
- The health effects assessment conducted by FSANZ concluded that current available evidence supports the plausibility of a bifidogenic effect of 2'-FL alone or in combination with LNnT, and a potential protective inhibitory effect of 2'-FL against invasive *Campylobacter jejuni* (*C.jejuni*).
- Assessment against two relevant Ministerial Policy Guidelines (Regulation of Infant Formula and Intent of Part 2.9 – Special Purpose Foods) conducted by FSANZ concluded that the addition of 2'-FL and LNnT to infant formula was consistent with the relevant ministerial policy guideline. FSANZ also noted that while the addition of these substances to FSFYC was not strongly aligned with the Code's definition of the food category, the addition is safe and permits alternative ingredients to GOS and IFT.

- FSANZ proposed to prescribe ingredient names for 2'-FL and LNnT for use on both infant formula and FSFYC labels. '2'-fucosyllactose' and 'Lacto-N-neotetraose', without the associated acronym, are the suggested prescribed names.
- Due to the purification process in the production of 2'-FL and LNnT, it is highly unlikely that these ingredients will contain novel protein or DNA. However, if novel protein is present, the product would require 'genetically modified' labelling as per Standard 1.5.2.

Summary of position

- **The departments do not support, at this time, the addition of 2'-FL and LNnT to infant formula.**
  - This is on the basis that it is not consistent with the Ministerial Policy Guideline on Regulation of Infant Formula Products.
  - The departments request further data on the safety of these two oligosaccharides at the levels proposed to be added to infant formula and stronger evidence to substantiate the benefit of their addition to infant formula. The departments are of the view that a plausible relationship between the oligosaccharides and certain health effects is not equivalent to a substantiated health benefit.
  - Further labelling restrictions are required to prevent reference to human milk on infant formula, including restrictions on the use of the abbreviation 'HMO'.
- **The departments do not support the preliminary view to permit the voluntary addition of 2'-FL and LNnT to FSFYC.**
  - This is on the basis that the addition is not consistent with the Ministerial Policy Guideline for the Intent of Part 2.9 – Special Purpose Foods, in particular with the principle that the composition of the special purpose food should be consistent with the intended purpose.
  - The likelihood for the cross promotion of these oligosaccharides infant formula through 'line marketing' is also high, negating any associated restrictions on labelling and reference to human milk in infant formula .

Set out below is an explanation for the departments' position.

<u>Safety assessment of higher maximum permitted level than requested by Applicant</u>

The departments have reservations regarding the level of evidence used to support FSANZ's concluded safety of the proposed higher maximum level of 2'-FL. We are particularly concerned that the evidence base does not include any studies at the proposed higher level in the target population (infants and young children). It is recognised that, in theory, the higher permitted level of 2'-FL is expected to be safe, as it is within the range reported to be found in human breastmilk. However, this permission is for microbially produced, human milk identical 2'-FL and LNnT. These synthetically produced substances do not have a history of safe use in Australia and New Zealand, and there is some risk in extrapolating the safety assessment using evidence

from human milk consumption in which these oligosaccharides are two of 200 different oligosaccharides which collectively and synergistically impact on gut flora[1].

The Ministerial Policy Guideline on the Regulation of Infant Formula Products (infant formula policy guidelines) notes the physiological vulnerability of infants, and the specific order principles within the guidelines state that infant formula regulation should recognise this vulnerability. Extrapolation of human milk and breastfed infant health data to determine safety introduces some uncertainty and as such is not aligned with this principle. We request additional evidence is provided for the safety of the higher proposed maximum permitted level when added to infant formula and given to infants before such a level is permitted.

Evidence of substantiated health benefit

The infant formula policy guidelines state that substances subject to pre-market assessment for use in infant formula and follow on formula (which would include human milk identical 2'-FL and LNnT) should have a **substantiated** beneficial role in normal growth and development, and that **'particular caution should be applied by the Authority where such links are less clear'**.

The departments question whether the evidence available is sufficient to **clearly substantiate** a health benefit of 2'-FL and LNnT. The evidence for the anti-infective effect against invasive *C.jejuni* is particularly weak, with the health effects assessment including mostly in vitro and animal studies, and only one observational study in humans (Morrow et. al 2004)[2]. Further, the validity of the results of the only human study are questionable due to several study limitations. Most significantly, the identified association is based on the ratio of 2'-FL to total Human Milk Oligosaccharides (HMOs), rather than the quantity of 2'-FL, and thus the extent of the anti-infective effect cannot be established at the proposed levels. Additionally, the study was conducted in Mexico approximately 20 years ago, which raises questions of applicability to the Australian and New Zealand population.

Similarly, there are some limitations of the evidence included to support the suggested bifidogenic effect of 2'-FL and LNnT. Specifically, control of confounding factors was not discussed for many studies included in the health effects assessment. As human microbiota composition is dependent on a range of factors[3,4], regard should be given to the quality of evidence (particularly control of confounding) when assessing this proposed health effect.

The departments also note that some studies included to support a bifidogenic effect did not measure 2'-FL and LNnT and would not be appropriate to include in the evidence

[1] Smilowitz, J.T., Lebrilla, C.B., Mills, D.A., German, J.B. and Freeman, S.L. (2014) Breast milk oligosaccharides: structure-function relationships in the neonate. *Annual review of nutrition*, *34*, pp.143-169.
[2] Morrow AL, Ruiz-Palacios GM, Altaye M, Jiang X, Guerrero ML, Meinzen-Derr JK, Farkas T, Chaturvedi P, Pickering LK, Newburg DS (2004) Human milk oligosaccharides are associated with protection against diarrhea in breast-fed infants. J Pediatr 145:297–303.
[3] Davis EC, Wang M, Donovan SM (2017) The role of early life nutrition in the establishment of gastrointestinal microbial composition and function. Gut Microbes 8:143–171.
[4] Milani C, Duranti S, Bottacini F, Casey E, Turroni F, Mahony J, Belzer C, Delgado Palacio S, Arboleya Montes S, Mancabelli L, Lugli GA, Rodriguez JM, Bode L, Vos W de, Gueimonde M, Margolles A, van Sinderen D, Ventura M (2017) The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. Microbiol Mol Biol Rev 81.

base. For example, although Bezitzogolou (2011)[5] and Tannock et. al (2013)[6] found evidence for a bifidogenic effect in exclusively breastfed infants (and such infants would be more likely to consume 2'-FL and LNnT) compared with formula-fed infants, there may be several other beneficial components present in breastmilk which could also explain the observed effect.

Overall, the available evidence suggests **plausible** relationships between 2'-FL, LNnT and some health effects, however the departments do not consider this as synonymous with a **substantiated** health benefit (as specified in the infant formula policy guidelines). This view is similar to Plaza-Diaz et al (2018)[7] which noted that many proposed health benefits of HMOs *'have not been substantiated in the few randomized, double-blinded, multicenter controlled trials that are available'*. The authors also suggest that the addition of selected HMOs to infant formula products does not consider the role of the many other HMOs present in human milk. This supports the need for further controlled trials, which can test the health benefits of 2'-FL and LNnT as consumed in manufactured food products.

Based on the available evidence, **the departments do not believe the proposed addition of 2'-FL and LNnT to infant formula is consistent with the relevant policy guidelines**. If safety at the proposed levels in formula fed infants can be demonstrated, together with stronger evidence to demonstrate a substantiated benefit (rather than a plausible one) in formula fed infants, the departments would support the voluntary addition of 2'-FL and LNnT to infant formula. With provision of this evidence, the application would merit progression for infant formula on the basis that the specific order principles of the policy guidelines would be satisfied in their entirety.

Labelling of 2'-FL and LNnT in infant formula

While the departments support the prescribed names of these oligosaccharides to prevent reference to human milk, further limitations to labelling would be required to limit reference to these oligosaccharides as human milk oligosaccharides, such as the use of 'HMO'.

Addition of 2'-FL and LNnT to FSFYC/ toddler milk

The addition of 2'-FL and LNnT to FSFYC does not appear to be sufficiently justified. FSFYC are formulated supplementary foods used to address situations where intakes of energy and nutrients may not be adequate to meet requirements. The Applicant notes that the intended purpose of FSFYC is to supplement the energy and nutrient requirements of growing children and those with 'fussy eating' behaviours, and that the addition of 2'-FL and LNnT would increase the consumption of HMOs. However, as breastmilk composition is not the primary reference for FSFYC, the addition of 2'-FL and LNnT does not fulfil the intended purpose of nutritional supplementation. While these

[5] Bezirtzoglou E, Tsiotsias A, Welling GW (2011) Microbiota profile in feces of breast- and formula-fed newborns by using fluorescence in situ hybridization (FISH). Anaerobe 17:478–482.
[6] Tannock GW, Lawley B, Munro K, Gowri Pathmanathan S, Zhou SJ, Makrides M, Gibson RA, Sullivan T, Prosser CG, Lowry D, Hodgkinson AJ (2013) Comparison of the compositions of the stool microbiotas of infants fed goat milk formula, cow milk-based formula, or breast milk. Appl Environ Microbiol 79:3040–3048.
[7] Plaza-Díaz J, Fontana L, & Gil A (2018). Human Milk Oligosaccharides and Immune System Development. *Nutrients*, *10*(8), 1038.

products are currently permitted to contain galacto-oligosaccharides, this permission was granted prior to the Ministerial Policy Guideline on Intent of Part 2.9 – Special Purpose Foods.

This Guideline notes that Part 2.9 of the Code (including FSFYC) is intended to prescribe specific requirements for physiologically vulnerable groups, and that food standards within Part 2.9 are prescribed relative to the particular intended dietary use of the food. This is further reiterated in the specific order principle that 'the composition of special purpose food should be consistent with the intended purpose'. The addition of 2'-FL and LNnT does not support the intended purpose specified by the Applicant, and is inconsistent with the policy guidelines.

A significant risk of permitting 2'-FL and LNnT in FSFYC is the likelihood for cross promotion of infant formula through 'line marketing'. This is the use of near identical packaging for FSFYC and infant formula and marketing FSFYC as one of the stages of infant formula with infant formula as Stage 1, follow-on formula as Stage 2 and toddler milk as Stage 3. Line marketing is a recognised means of promoting infant formula and circumventing the prohibitions on making claims about and advertising infant formula[8,9]. While cross promotion of infant formula through FSFYC is an existing issue, the significance of this risk in products containing 2'-FL and LNnT is of greater concern due to the human milk identical nature of 2'-FL and LNnT and the demonstrated marketing of these as human milk oligosaccharides on overseas markets.

We are aware that in several international markets, toddler milk products containing 2'-FL and LNnT are labelled with 'Human Milk Oligosaccharides' and 'HMO' (see images below). As nutrient content and health claims are permitted on FSFYC in Australia and New Zealand, it is very possible that these products could be labelled as 'contains Human Milk Oligosaccharides' and infant formula could be labelled 'HMO'. As these products are sold alongside each other, an average consumer may quickly link the two products and the infant formula may be inferred to contain human milk ingredients, possibly implying equivalence to human milk. Such promotion would contradict the infant formula policy guidelines which state that the labelling of infant formula should not be represented as equivalent to, or better than breastmilk.

It is noted that FSANZ proposes to prescribe the ingredient names for 2'-FL and LNnT on infant formula and FSFYC. However, the department's understanding is that these prescribed names would not prevent nutrient content (or health) claims similar to those observed in other countries such as 'Contains Human Milk Identical Oligosaccharides'.

On this basis, the departments **do not support the preliminary view to permit the voluntary addition of 2'-FL and LNnT to FSFYC**.

If permission were to be granted, the departments note that additional labelling measures would be required to ensure products containing 2'-FL and LNnT are not

[8] Berry, N., S. Jones, and D. Iverson, Toddler milk advertising in Australia: the infant formula ads we have when we don't have infant formula ads., in ANZMAC Annual Conference 2010: Australian and New Zealand Marketing Academy Conference 2010. 2010, P. Ballantine & J. Finsterwalder (Eds.): Christchurch, New Zealand.

[9] The Australian Competition and Consumer Commission July 2016 Final Determination: Application for revocation of authorisations A90539 and A90540 and substitution with authorisations A91506 and A91507 for the Marketing in Australia of Infant Formula: Manufacturers and Importers Agreement

promoted or inferred (either directly or indirectly) as being from or equivalent to human milk. This may require explicit prohibition of the term 'Human Milk Oligosaccharides' and 'HMO'.

<u>International products containing HMOs</u>


Abbott
NO ARTIFICIAL GROWTH HORMONES*
NON-GMO
1 cup a day
toddler drink
BEBIDA PARA NIÑOS
go & grow
by Similac®
12-36
IMMUNE SUPPORT
BRAIN & EYE DEVELOPMENT
LUTEIN
VITAMIN E
2'-FL
HMO
Human Milk Oligosaccharide‡
‡not from human milk
DHA
MILK-BASED POWDER
POLVO A BASE DE LECHE
NET WT./PESO NETO
24 OZ (1.5 LB)