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

Due date of submission – 2 September 2019

The Victorian Departments of Health and Human Services and Jobs, Precincts and Regions (the departments) welcome the opportunity to respond to this second Call for Submissions 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). The Application has been submitted by Glycom A/S (the Applicant).

The departments recognise that breastfeeding is the healthiest and recommended way of feeding infants and that the regulation of infant formula has implications for the health outcomes of formula-fed infants and breastfeeding rates. Our submission is underpinned by the Ministerial Policy Guideline – Regulation of Infant Formula Products, which places the health and safety of infants at the centre of decisions for infant formula regulation. The policy guideline conveys ministers' expectations that a higher bar be set for infant formula regulations than other foods.

Infants are particularly vulnerable due to their immature systems and the reliance on infant formula as the sole, or significant source of, nutrition. It is recognised that care is needed to avoid burdening infants' metabolism with unnecessary substances or unnecessarily large amounts of substances in infant formula[1],[2].

The departments:

1. **Do not support the addition of 2'-FL and LNnT to infant formula in the absence of adequate evidence**. This proposed amendment is not consistent with existing Ministerial Policy Guideline and FSANZ has not sufficiently demonstrated the protection of public health and safety at the proposed levels.
2. **Do not support the addition to FSFYC**. This proposed amendment is not consistent with the relevant Ministerial Policy Guideline which states that the composition of the special purpose food should be consistent with the intended purpose.

In addition, the departments are concerned more broadly about the level of evidence deemed acceptable by FSANZ and its stated views that evidence of possible or plausible effects is sufficient to meet the criteria of a 'substantiated beneficial role in the normal growth and development of infants'.

[1] Koletzko, B., et al., *Global standard for the composition of infant formula: recommendations of an ESPGHAN coordinated international expert group.* Journal of Pediatric Gastroenterology and Nutrition, 2005. **41**(5): p. 584-599.

[2] EFSA (EFSA Panel on Dietetic Products Nutrition and Allergies), *Scientific opinion on the essential composition of infant and follow-on formulae.* EFSA Journal, 2014. **12**(7): p. 3760-3866.

At the first round of consultation, the departments' position was:

- The proposed addition of 2'-FL and LNnT to infant formula was not consistent with the relevant Ministerial Policy Guidelines. If safety at the proposed levels in formula-fed infants could be demonstrated, together with stronger evidence to demonstrate a substantiated health 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.
- The addition of 2'-FL and LNnT to FSFYC was not supported because it did not meet the relevant policy guideline (Intent of Part 2.9; that the composition of special purpose food should be consistent with the intended purpose) and because of the risk of these products being used to circumvent marketing restrictions on infant formula.

The response from FSANZ included in the second Call for Submissions has not adequately addressed these concerns.

Rationale

Addition of 2'-FL and LNnT to infant formula

Safety

The safety of 2'-FL up to 2.4g/L has not been demonstrated in the target population.

FSANZ is proposing to permit 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 in infant formula. The departments agree that, based on toxicity studies and short-term feeding studies, there do not appear to be safety concerns with the addition of LNnT at a maximum of 0.6g/L and 2'-FL at a maximum at 1.2 g/L. However, FSANZ is proposing to permit 2'-FL up to a maximum which is twice the level tested in studies. While the proposed permitted levels are theorised to be safe, FSANZ has not demonstrated the safety of this maximum permission in the target population.

Benefit to infants

The departments consider that the evidence presented in the Application does not support, on balance, that 2'-FL and LNnT have a beneficial role in the normal growth and development of infants when added to infant formula. The mere presence of a substance in human milk does not necessarily indicate a specific benefit of this substance for the infant[3].

Under the policy guideline for the regulation of infant formula products:

> *j) Substances subject to pre-market assessment for use in infant formula and follow-on formula* ***should have a substantiated beneficial role in the normal growth and development of infants or children****, or a technological role, taking into account, where relevant, the levels of comparable substances in breastmilk. A substance's role in normal growth and development* ***is substantiated where there is appropriate evidence to link the physiological, biochemical and/or functional effects of the substance to specific health outcomes*** *for infants, in infancy or childhood. Particular caution should be applied by the Authority where such links are less clear.*

The Applicant proposed three health effects of 2'-FL and LNnT: 1) an anti-infective effect, 2) a beneficial health effect on immune modulation, intestinal barrier function and allergic response and 3) a bifidogenic effect.

[3] EFSA (EFSA Panel on Dietetic Products Nutrition and Allergies), *Scientific opinion on the essential composition of infant and follow-on formulae.* EFSA Journal, 2014. **12**(7): p. 3760-3866.

1. Anti-infective effect:

The departments do not believe that FSANZ has presented adequate evidence to link the physiological, biochemical and/or functional effects of 2'-FL and LNnT to this specific health outcome for infants.

The evidence provided for the anti-infective effect against invasive *Campylobacter jejuni* relies on *in vitro* studies looking at the ability of 2'-FL or LNnT to bind with *C. jejuni* preferentially over cell lines, and animal studies using 2'-FL only and in very high doses; levels not consistent with the proposed levels in infant formula.

The only study presented involving infants used breastfed infants to demonstrate an anti-infective effect, not a formula containing 2'-FL or LNnT[4]. This study showed a correlation between the percentage of 2'-FL relative to total oligosaccharides in breastmilk and the rate of *Campylobacter*-related diarrhoea in the infants. In the study, breastmilk contributed only 49% of feeds; babies were also given formula, as well as other foods. Given the varied diets of these infants and the numerous protective elements in breastmilk, it is not scientifically valid to assign causation to one component of the breastmilk, nor to extrapolate this effect to the addition of this component to infant formula. FSANZ's conclusion that a health effect relating to 2'-FL and *Campylobacter* diarrhoea *could* occur does not amount to a substantiated beneficial role and is insufficient to justify the addition to infant formula.

2. Beneficial health effect on immune modulation, intestinal barrier function and allergic response:

The departments agree with FSANZ's assessment that these health effects are not supported by the evidence presented.

3. Bifidogenic effect:

The departments consider the evidence presented inadequate to link the physiological, biochemical and/or functional effects of 2'-FL and LNnT to specific health outcomes for infants.

The departments expect that adequate evidence would:

A. show that the addition of 2'-FL and LNnT at the proposed levels to infant formula would produce a physiological, biochemical or functional effect, such as a specific bifidogenic effect in formula-fed infants and then

B. show that the resulting bifidogenic effect resulted in specific health outcomes for infants.

We consider that FSANZ has not provided adequate evidence to demonstrate either of these steps.

A. Physiological, biochemical or functional effect: bifidogenic effect in formula-fed infants

FSANZ has not clearly defined the specific physiological, biochemical or functional effect expected by adding 2'-FL and LNnT to infant formula or demonstrated that the desired effect is produced when 2'-FL and LNnT is added to infant formula.

The majority of the evidence provided by FSANZ to support a bifidogenic effect from infant formula containing 2'-FL or LNnT relies on breastmilk and its observed effect on the

[4] 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.

microbiota of breastfed infants (given breastmilk contains LNnT and 2'-FL, in 65-80% of women). In addition, rather than producing a general bifidogenic effect, the evidence suggests the effect of human milk oligosaccharides in breastmilk is to encourage only certain types of *Bifidobacteria*.

The evidence also shows that the development of gut microbiota in breastfed infants and into childhood is complex. The role of the more than 200 different oligosaccharides in human milk is still not well understood[5]. Bacteria within breastmilk itself (including *Bifidobacteria*) have also been shown to influence the resulting microbiota of the infant gut[6,7]. Furthermore, while the presence of *Bifidobacteria* differs between breastfed and formula-fed infants, the amount and types of *Bifidobacteria* also differ between breastfed infants; infants of mothers who secrete one type of human milk oligosaccharides have different amounts and types of *Bifidobacteria* than mothers who do not secrete these types of human milk oligosaccharides. The bifidogenic effect expected by adding 2'-FL and LNnT to infant formula has not been clearly defined; whether it be a general bifidogenic effect or a specific bifidogenic one.

FSANZ has also not adequately demonstrated that the desired bifidogenic effect is produced when 2'-FL and LNnT is added to infant formula. FSANZ described only one study which looked at the gut microbiota of infants fed a formula containing 2'-FL and LNnT. FSANZ reported this formula resulted in a microbial composition 'more similar' to that of breastfed infants. Given the diversity of *Bifidobacteria* across the breastfed cohort it is not clear how this was defined, and it is not possible to assess these results because they were provided commercial-in-confidence by the Applicant.

B. Linking the physiological, biochemical and/or functional (bifidogenic) effect of the substance to specific health outcomes for infants.

No evidence has been provided to demonstrate that the alleged bifidogenic effect (or selective bifidogenic effect) of 2'-FL and LNnT results in specific health outcomes for infants. FSANZ indicated it was unnecessary to provide evidence of a health outcome for the specific bifidogenic effect of these two oligosaccharides because it has 'previously recognised (under Proposal P306 and Application A1055) that the dominance of *Bifidobacterium* in the intestinal microflora is generally considered to be beneficial to the host'. The departments consider that neither P306 nor A1055 provided sufficient evidence of a health benefit of a bifidogenic effect, or that these assessments could serve to demonstrate a health benefit of 2'-FL and LNnT:

- *Proposal P306 - Addition of inulin/FOS & GOS to Food*

A review of P306 reveals FSANZ stated that while concern was expressed by submitters that there was insufficient evidence to demonstrate benefit/efficacy in infant formula products, infant foods and formulated supplementary foods for young children, FSANZ has, in the absence of ministerial policy guidance, confined the risk assessment to consider safety. It stated: 'health benefits attributed to the substance

[5] Zivkovic, Angela M et al. (2011) "Human milk glycobiome and its impact on the infant gastrointestinal microbiota." *Proceedings of the National Academy of Sciences of the United States of America* vol. 108 Suppl 1,Suppl 1.

[6] Gronlund, M. M. et al. (2007) Maternal breast-milk and intestinal bifidobacteria guide the compositional development of the Bifidobacterium microbiota in infants at risk of allergic disease. Clin Exp Allergy 37, 1764–1772.

[7] Murphy, K., et al. (2017). "The Composition of Human Milk and Infant Faecal Microbiota Over the First Three Months of Life: A Pilot Study." Scientific Reports **7**: 40597.

when added to infant formula have not been considered in the risk assessment of this Proposal'[8].

- *Application A1055 - Short-chain Fructo-oligosaccharides*

In Application A1055, FSANZ considered extending the permission for inulin-derived oligosaccharides to include related short chain fructo-oligosaccharides (FOS). FSANZ presented studies with formula using these FOS, many of which showed no effect on the levels of *Bifidobacteria* in infants' guts. The health effect assigned to these ingredients was the ability to soften stools and reduce the incidence of constipation, rather than the bifidogenic effect *per se*.

Discussions of *Bifidobacteria* in P306 and A1055 were also limited to the genus *Bifidobacteria*, not the subspecies. In the current Application A1155, the premise of using 2'-FL and LNnT is based on these compounds promoting certain subspecies of *Bifidobacteria* over others (e.g. *B. longum* subsp. infantis, rather than *B. adolescentis* which is the major species found in adult faeces). FSANZ has not provided evidence that either the increase in *Bifidobacteria* more broadly, or the specific subspecies promoted by the presence of 2'-FL and LNnT in infant formula, have a beneficial effect in formula fed infants.

Recent reviews of human milk oligosaccharides note that many proposed health benefits of human milk oligosaccharides have not been substantiated in the few randomized, double-blinded, multicenter controlled trials that are available. The addition of selected human milk oligosaccharides to infant formula products does not consider the role of the many other human milk oligosaccharides present in human milk and further research is needed[9,10]. This supports the need for further controlled trials, which can test the health benefits of 2'-FL and LNnT when added to infant formula.

In summary, the departments consider that FSANZ has not provided sufficient evidence to demonstrate that the addition of 2'-FL and LNnT to infant formula results in a specific physiological, biochemical and/or functional effect in infants receiving this formula, or that these effects are linked to specific health outcomes for these infants.

Labelling of 2'-FL and LNnT in infant formula

If further evidence was provided to support the safety and health benefits to infants of consuming formula with 2'-FL and LNnT at the proposed levels, the departments would support FSANZ's proposed prohibition on the use of the terms (or related terms or acronyms) 'human milk/ human milk-identical oligosaccharides'.

This application has revealed industry's intention to use 'human milk-identical' type labels on ingredients in infant formula (and toddler milks). Concerns about this labelling extend beyond oligosaccharides to all potential ingredients added to formula (many of which may currently be chemically identical to those in breastmilk). Now this marketing intention is known, the Standard should be future-proofed to generally prohibit the terms human milk-identical or similar, including acronyms, rather than limit this prohibition specifically to

[8] Final Assessment Report P306 - Addition of inulin/FOS & GOS to Food, p85, http://www.foodstandards.gov.au/code/proposals/documents/P306%20FOS%20_%20GOS%20FAR%20FINALv2.pdf

[9] Plaza-Díaz J, Fontana L, & Gil A (2018). Human Milk Oligosaccharides and Immune System Development. *Nutrients*, *10*(8), 1038.

[10] Doherty, A. M., Lodge, C. J., Dharmage, S. C., Dai, X., Bode, L., & Lowe, A. J. (2018). Human Milk Oligosaccharides and Associations with Immune-Mediated Disease and Infection in Childhood: A Systematic Review. *Frontiers in pediatrics*, *6*, 91. doi:10.3389/fped.2018.00091

oligosaccharides. This is also consistent with good drafting principles, to prevent the future creation of a list of prohibited terms for 'human milk-identical' ingredients.

Further work is also required to ensure these prohibitions will not be circumvented by mechanisms such as trademarks.

Addition to Formulated supplementary foods for young children (FSFYC)

The departments do not support the addition of 2'-FL and LNnT to FSFYC on the basis that it is not consistent with the purpose of these special purpose foods, as specified in the associated policy guideline. FSFYC are formulated supplementary foods used to address situations where intakes of energy and nutrients may not be adequate to meet requirements. Unlike infant formula, the composition of these products does not rely on breastmilk as a primary reference. The departments do not believe the addition of human milk identical oligosaccharides, 2'-FL and LNnT, supports supplementing an inadequate food intake in young children.

On page 82 of Supporting Document 1, FSANZ states that infants develop a more adult-like microbiota by one year of age. FSANZ has not explained or demonstrated how adding 2'-FL and LNnT to FSFYC, to promote a breastfed infant-type microbiota rather than a microbiota more consistent with children and adults, is appropriate or consistent with the purpose of supplementing inadequate food intake in young children.

The departments do not agree that 2'-FL and LNnT provide alternatives to existing permissions for plant-based oligosaccharides in FSFYC. FSANZ indicates the *Bifidobacteria* subspecies that dominate in children and adults have been shown to be promoted by plant-based oligosaccharides, normally provided through food. In contrast, the assessment discusses that the *Bifidobacteria* spp. promoted by 2'-FL and LNnT do not appear to be promoted by plant-based oligosaccharides. Where there is inadequate food intake, children are likely to be consuming insufficient plant fibre. Adding plant-based oligosaccharides to FSFYC to promote age-appropriate *Bifidobacteria* is consistent with supplementing inadequate food intake in this age group. Adding 2'-FL and LNnT is not.

Labelling of FSFYC

In addition to not being suitable for FSFYC, permissions for 2'-FL and LNnT in FSFYC pose a risk for cross-marketing of infant formula. It has been recognised that FSFYC, which does not have the same prohibitions on labelling, claims and references to breastmilk, or humanising elements, is an established platform for the marketing of infant formula[11]. While FSANZ has responsibly proposed prohibiting the use of the terms 'human milk oligosaccharides' or related acronyms or terms on FSFYC, there remain avenues for the industry to market these ingredients as being 'related to' breastmilk, such as through trademarks, with the subsequent cross-marketing to infant formula. These need to be addressed. In addition, consistent with the comments under infant formula labelling, the departments suggest terms implying human milk-identical should be prohibited more generally on FSFYC rather than being limited to oligosaccharides should these be permitted.

[11] 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.