

20 December 2019

[106-19]

Supporting document 2

Assessment against Ministerial Policy Guidelines (at Approval)

Application A1155 - 2'-FL and LNnT in infant formula and other products

FSANZ has had regard to two Ministerial Policy Guidelines relevant to application A1155, as required under subsection 18(2) of the FSANZ Act:

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

The tables below summarise our assessment against the specific policy principles of these policy guidelines. The tables have been revised since the 2nd Call for Submissions (CFS), following consideration of submissions and targeted consultation.

1 Regulation of Infant Formula Products

In reaching our decision FSANZ has had regard to the policy guideline on the Regulation of Infant Formula Products. The table below summarises our assessment against the specific policy principles (not in alphabetical order) for the proposed addition of 2'-FL alone and in combination with LNnT to infant formula products (includes infant formula, follow-on formula and infant formula for special dietary use).

Specific Policy Principles	Assessment
(a) The regulation of infant formula products should recognise that breastfeeding is the normal and recommended way to feed an infant.	FSANZ acknowledges that breastfeeding is the recommended way to feed an infant.
(b) The regulation of infant formula products should not be inconsistent with the national nutrition policies and guidelines of Australia and New Zealand that are relevant to infant feeding.	The proposed voluntary addition of 2'-FL and LNnT is not inconsistent with current national nutrition policies and guidelines for infant feeding.
(h) The composition of breast milk should be used as a primary reference for determining the composition of infant formula and follow-on formula.	<p>The composition of breast milk was a primary reference for determining the compositional limits. Oligosaccharides make up a large component of the carbohydrate content of breast milk. 2'-FL is secreted by the majority of women worldwide and LNnT is always present in human milk. The natural occurrence of 2'-FL and LNnT in human milk was examined (see SD1) noting the range of concentrations present in mature human milk are 1.0 – 3.6 g/L for 2'FL and 0.04 – 1.08 g/L for LNnT.</p> <p>For comparison, the proposed maximum for 2 'FL alone or in combination with LNnT is 2.4 g/L which is considerably lower than levels in human milk and previously approved maximums for galacto-oligosaccharides (GOS) and inulin-type fructans (ITF). These latter oligosaccharides contrast with 2' FL and LNnT because they are not present in human milk or only present in trace amounts.</p>
(c) The regulation of infant formula products should be based on risk analysis, taking into account the vulnerability of the population for whom they are intended and the importance of these products in the diets of formula fed infants.	<p>Infants are recognised as a vulnerable population group, hence infant formula is tightly regulated in the Code. FSANZ has used the internationally accepted risk analysis framework in our decision making, this takes into account the importance of the role of formula as a potential sole source of nutrients and the vulnerability of the formula-fed infant population.</p> <p>The risk and technical assessment component of the risk analysis comprised:</p> <ul style="list-style-type: none"> (i) a food technology assessment of 2'-FL and LNnT; (ii) a safety assessment to identify potential adverse effects associated with 2'-FL and LNnT; (iii) a dietary intake assessment to estimate the total dietary intake of 2'-FL and LNnT for breastfed infants and intake resulting from the addition of 2'-FL and LNnT to infant formula products and FSFYC; and (iv) an assessment of the stated health effects. <p>The risk management component comprised:</p> <ul style="list-style-type: none"> (i) consideration of risk assessment conclusions (ii) labelling to manage potential risks and provide adequate information

Specific Policy Principles	Assessment
	<ul style="list-style-type: none"> (iii) appropriate conditions for use: maximum use, minimum levels, specifications (iv) issues raised by submitters (v) international consistency and harmonisation (vi) policy guidelines <p>The conclusions of the assessments were also made taking into account all best available evidence.</p>
<p>(d) The composition of infant formula must be safe, suitable for the intended use and must strive to achieve as closely as possible the normal growth and development (as measured by appropriate physiological, biochemical and/or functional outcomes) of healthy full term exclusively breastfed infants when infant formula used as the sole source of nutrition up to six months of age.</p> <p>AND</p> <p>(e) The composition of follow-on formula must be safe, suitable for the intended use and must strive to achieve as closely as possible the normal growth and development (as measured by appropriate physiological, biochemical or functional outcomes) of healthy full term breastfed infants at the appropriate age when follow-on formula used as the principal source of liquid nourishment in a progressively diversified diet.</p>	<p>FSANZ considered an evidence base which included <i>in vitro</i> evidence, animal studies, infant trials as well as other relevant studies for this assessment. This evidence base demonstrates that these oligosaccharides are safe and suitable for use in infant formula products.</p> <p>In relation to safety:</p> <ul style="list-style-type: none"> • Glycom's 2'-FL and LNnT are chemically and structurally identical to the naturally occurring substances in human milk. • Intestinal absorption of 2'-FL and LNnT is limited. • No adverse effects were observed at high doses in suitable animal studies of an appropriate age, or at levels in infant studies. • Taken together, this evidence is sufficient to conclude that there are no public health and safety concerns associated with the addition of 2'-FL alone or in combination with LNnT at the proposed concentrations. <p>Normal growth has been considered, noting measures of growth relate to both safety and favourable health effects. Given the complexities and ethical challenges in infant feeding research, FSANZ notes that comparisons of anthropometric measures (length, weight, head circumference) should consider: control and intervention groups as well as intervention groups and breastfed reference group. The assessment included infant studies which assessed growth concluding that there are no negative impacts on physical growth throughout infancy.</p> <p>Normal development has also been considered. The policy guideline specifies that development is to be measured by appropriate physiological, biochemical and/or functional outcomes. The decision to permit 2'-FL and LNnT also considered that:</p> <ul style="list-style-type: none"> • Breastfed infants are the reference standard for the normal healthy development of gut microflora in infants. Breastfed infants have different stool microflora and metabolic profile when compared to formula-fed infants; breastfed infants typically have a higher relative abundance of bifidobacteria compared to formula fed infants.

Specific Policy Principles	Assessment
	<ul style="list-style-type: none"> • It is appropriate to compare the relevant physiological, biochemical or functional effect(s) in a control and intervention group, and between an intervention group and a breastfed reference group • The evidence assessed substantiates there is a bifidogenic effect resulting from inclusion of 2'-FL and LNnT in infant formula propoducts. The stool microflora and metabolic profile shift towards those of breastfed infants. These are appropriate functional outcomes given the documented differences in the stool microbiota between breastfed and formula-fed infants. • The evidence from cell culture and animal studies substantiates a specific binding mechanism for 2'-FL and invasive strains of <i>Campylobacter jejuni</i> and a biologically plausible mechanism for an inhibitory effect against invasive <i>C. jejuni</i> infection. As it is not ethical to conduct human clinical trials in infants to demonstrate the protective effects of 2'-FL in reducing severity of invasive <i>C. jejuni</i> infection FSANZ considers the
(f) The essential composition of infant formula and follow-on formula should be prescribed in regulation and must satisfy the nutritional requirements of infants.	Not applicable to this application as the proposed permission is voluntary.
(g) Compositional requirements for infant formula and follow-on formula products should only be mandated in regulation where there is sufficient evidence to demonstrate that they are safe and essential for normal growth and development of infants.	Not applicable to this application as the proposed permission is voluntary.
(i) Pre-market assessment, relative to principles (d) and (e), should be required for any substance proposed to be used in infant formula and follow-on formula that: <ul style="list-style-type: none"> i. does not have a history of safe use at the proposed level in these products in Australia and New Zealand; or ii. has a history of safe use in these products in Australia and New Zealand, but which, having regard to source, has a different form/structure, or is produced using a substantially different technique or technology. 	A comprehensive pre-market assessment was undertaken because 2'FL and LNnT derived from GM technology do not have a history of safe used in Australia and New Zealand. Our conclusions are summarised section 2.2.1, 2.2.2 and 2.2.3 of the Approval report.

Specific Policy Principles	Assessment
<p>(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 breast milk.</p> <p>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.</p> <p>Particular caution should be applied by the Authority where such links are less clear.</p>	<p>Particular caution has been applied to the assessment. When considering the applicants suggested physiological, biochemical and/or functional effects of the substances and specific health outcomes, FSANZ concluded there is limited evidence to support a substantiated role of 2'-FL and LNnT for the following health effects: immune modulation, improved barrier function and alleviation of allergic responses.</p> <p>The assessment determined that evidence substantiates a specific binding mechanism; whereby 2'-FL mimics the intestinal binding site of invasive campylobacter and inhibits binding, resulting in potential for reduction in severity of an invasive <i>C. jejuni</i> infection. The assessment also concludes this effect is limited to the 2'FI and invasive strains of <i>C. jejuni</i>.</p> <p>As explained in the report micro section, this is nearly impossible to do from these effects.</p> <p>However, taken together, the identical nature and levels of these oligosaccharides at found in human milk, and the demonstrated favourable health effects consistent with a voluntary compositional permission, FSANZ concluded that permitting the addition of 2'-FL alone or combined with LNnT, would provide potential beneficial health outcomes in infants.</p>
<p>(k) The labelling and advertising of infant formula products should be consistent with the World Health Organization International Code of Marketing of Breast Milk Substitutes as implemented in Australia and New Zealand.</p>	<p>Existing labelling requirements which would apply to the proposed addition of 2'-FL and LNnT support this specific policy principle (see section 2.3.4 of the Approval report for existing labelling requirements).</p> <p>A specific prohibition of terms such as 'human milk identical oligosaccharide' is proposed – see further comments to specific principle (l) below.</p>
<p>(l) The labelling and advertising of infant formula products should not represent those products as an equivalent to, or better than, breast milk.</p>	<p>FSANZ has specifically prohibited reference to 'human milk identical oligosaccharide', 'human milk oligosaccharide', 'HMiO' or 'HMO' (or words or abbreviations of similar effect) on infant formula products. The permitted approach allows use of the abbreviated chemical name/acronym or the generic term 'oligosaccharides'.</p> <p>Although the intent of subsection 2.9.1—24(c) of the Code is to prohibit such terminology on the label of infant formula products, FSANZ considers a specific prohibition would communicate more clearly that such terminology is inconsistent with specific policy principle (l).</p>
<p>(m) The labelling and advertising of infant formula products should provide information on the appropriate and safe use of those products.</p>	<p>The proposed voluntary addition of 2'-FL and LNnT to infant formula products would be subject to existing labelling requirements in Standard 2.9.1 which provide information on the safe and appropriate use of infant formula products.</p>

Specific Policy Principles	Assessment
<p>(n) The Authority should:</p> <ul style="list-style-type: none"> i. ensure that the prohibitions and restrictions on nutrient content, health, therapeutic, and prophylactic claims in the Food Standards Code are clear and effective for infant formula products; and ii. consider whether the current labelling regime is leading to consumers being misled about the quality or effectiveness of an infant formula product. 	<p>The existing labelling requirements, including the prohibition for nutrition content claims and health claims for infant formula products, would apply to the proposed addition of 2'-FL and LNnT.</p> <p>FSANZ has also specifically prohibited terminology such as 'human milk identical' (see policy principle (l) above) to avoid misleading consumers by the addition of 2'-FL and LNnT to infant formula products (the use of the generic term oligosaccharides is permitted).</p>
<p>(o) Infant formula products for special dietary use must be safe, suitable and meet the nutritional requirements to support the growth, development and dietary management of the infants for whom they are intended.</p>	<p>See comments for specific policy principles (d) and (j). FSANZ also notes that approval of 2'-FL and LNnT would provide alternative options to GOS and ITF currently permitted at higher levels for use in infant formula products which includes such products for special dietary use.</p>
<p>(p) The composition of infant formula products for special dietary uses should be based on appropriate scientific evidence.</p>	<p>FSANZ has used the best available scientific evidence to assess the application.</p> <p>The Code requirements for infant formula products for special dietary use (IFPSDU) provide a flexible approach, based on the composition of infant formula, to allow products formulated for particular conditions. Care is taken by food businesses to formulate products for specific dietary uses.</p>
<p>(q) The labelling and advertising of infant formula products for special dietary uses should clearly specify the special dietary or medical uses for which the product is intended.</p>	<p>Existing labelling requirements specific to IFPSDU would apply where products formulated for certain conditions are required to state the condition, disease or disorder for which the product has been formulated (sections 2.9.1—13 and 2.9.1—14 of the Code). No changes are proposed to these requirements.</p>

Specific Policy Principles	Assessment
Additional policy guidance - Expert Group	
<p>FSANZ should consider establishing an independent scientific expert group that may provide advise prior to pre-market assessment, based on scientific criteria established by the Authority, on whether:</p> <ol style="list-style-type: none"> i. a substance proposed to be added to infant formula products has a history of safe use in infant formula or follow-on formula in Australia and New Zealand; and ii. there is evidence available that the substance has a substantiated beneficial role in the normal growth and development of infants or children. 	<p>In response to concerns raised in submissions FSANZ sought advice on our assessment of the pathogen binding effect for <i>Campylobacter jejuni</i> and the bifidogenic effects from an expert microbiologist, Associate Professor Andrew Holmes¹. Assoc Prof Holmes noted the approach and conclusions reached by FSANZ were appropriate and reasonable. He also commented that FSANZ had taken a particularly cautious approach to our assessment of bifidogenic effect, noting the effect could be greater in infants who are predisposed to respond to the addition of these oligosaccharides in infant formula.</p> <p>FSANZ also sought advice from FSANZ Fellow Seppo Salminen on the assessment approach and conclusions, he supported the approach and conclusions of the assessment.</p> <p>On this basis FSANZ considers that an independent scientific group is not necessary for this application, noting that we have assessed the application using a risk analysis approach and applied particular caution in reaching our conclusions.</p> <p>See comments to specific policy principle (i) above.</p> <p>See comments to specific policy principle (j) above.</p>
Additional policy guidance -Relevant international ag	
<p>The regulation of infant formula products in Australia and New Zealand should be consistent to the greatest extent possible with:</p> <ul style="list-style-type: none"> • relevant World Health Organization agreements; and • relevant World Trade Organization agreements, Codex standards and guidelines 	<p>FSANZ has taken considerable account of the relevant WHO and WTO agreements and Codex standards and guidelines. The applicant's 2'-FL and LNnT are permitted and used in infant formula products sold in at least 37 overseas.</p> <p>The proposed addition supports international consistency and a competitive food industry (in accordance with high order policy principles 2(b) and (c)), providing trade opportunities.</p>

¹ Associate Professor Holmes specialises in the relationship between nutrition, gut microbiome and health and is the Microbiome Project node leader in the Charles Perkins Centre, and Co-leader of the Food for Health theme of the Centre for Advanced Food Enginomics at the University of Sydney.

2 Intent of Part 2.9 – Special Purpose Foods

FSANZ has had regard to the policy guideline on the Intent of Part 2.9 – Special Purpose Foods of the Code. The policy guideline includes specific and high order policy principles for standards contained within Part 2.9 of the Code. The table below summarises our assessment against the specific policy principles for the proposed addition of 2'-FL alone and in combination with LNnT to formulated supplementary foods for young children (FSFYC).

Specific Policy Principles	Assessment
a) Special purpose foods should be targeted to specific population groups who meet the criteria outlined in the policy guideline	This application does not amend the range of special purpose foods in Part 2.9 of the Code. Special purpose foods relevant to this application are infant formula products (as assessed against the specific policy above) and FSFYC.
b) The composition of special purpose food should be consistent with the intended purpose	<p>FSFYC are specifically formulated for children aged 1 to <4 years as a supplement to a normal diet to address situations where intakes of energy and nutrients may not be adequate to meet an individual's requirements.</p> <p>In assessing the proposed addition of 2'-FL and LNnT to FSFYC, FSANZ's first order priority was to ensure there are no public health and safety risks in accordance with subsection 18(1) of the FSANZ Act. FSANZ has also had regard to the relevant policy guideline in accordance with subsection 18(2) of the Act, as well as best available science, international consistency and industry trade and competition.</p> <p>FSANZ acknowledges that FSFYC are intended to supplement young children's diets when food intakes may be inadequate. However, the literature indicates that the diet in early childhood influences the continuing establishment of the gut microbiota (Mohammadkahah et al 2018; Robertson et al 2019). Oligosaccharides (as GOS & ITF) are already permitted in FSFYC and FSANZ's assessment concluded that 2'FL and LNnT having a bifidogenic effects and a pathogen inhibitory effect are biologically plausible, both of which may provide favourable health effects for young children (as for infants).</p> <p>FSANZ has assessed all available information provided by the applicant and from our own independent literature search, and did not identify evidence that would indicate the assessed anti-infective and bifidogenic effects would be limited to a particular age group of infants or toddlers. The addition is safe and provides potential beneficial health outcomes in toddlers.</p> <p>The proposed addition also supports international consistency and a competitive food industry (in accordance with high order policy principles 2(b) and (c)), and provides alternative options to ITF and GOS currently permitted at higher levels in FSFYC (see section 2.3.1 of the 2nd CFS).</p>

Specific Policy Principles	Assessment
<p>c) Adequate information should be provided, including through labelling and advertising of special purpose foods</p>	<p>The proposed voluntary addition to FSFYC would be subject to generic labelling requirements in the Code (see section 2.3.5 of the 2nd CFS report), and specific labelling requirements in Standard 2.9.3, Division 4. These existing requirements will enable consumers to make informed purchasing decisions.</p> <p>In addition to existing requirements, following consideration of submissions, FSANZ now proposes to specifically prohibit reference to 'human milk identical oligosaccharide', 'human milk oligosaccharide', 'HiMO' or 'HMO' (or words or abbreviations of similar effect) on FSFYC. The intent of this prohibition is to prevent consumers being misled or confused about the use of such terminology on FSFYC (see section 2.3.5.2 of the 2nd CFS report).</p>
<p>d) Consideration, where appropriate, should be given to application of controls to restrict access to a special purpose food on the basis of risk to public health and safety</p>	<p>Access to FSFYC on the market is currently not restricted. The safe addition of 2'-FL and LNnT to these foods does not warrant any change to these arrangements.</p>