Call for submissions – Application A1155 2'-FL and LNnT in infant formula and other products

Submission by SA Health (Department for Health & Wellbeing)

17 January 2019

SA Health welcomes the opportunity to comment on Application A1155 2'-FL and LNnT in infant formula and other products. SA Health has approached consideration of the issues raised in the 1st Call for submissions – Application A1155 with the aim of responding to the *Summary of FSANZ's preliminary position on regulatory measures* and in support of relevant components of the Ministerial Policy Guideline on *Infant Formula Products (IFP).*

In summary:

- **SA Health does not support development of a food regulatory measure to permit voluntary addition of 2'-FL and LNnT to infant formula and formulated supplementary food for young children (FSFYC) on the basis that the evidence provided does not constitute 'appropriate evidence' for the proposed health benefits of a bifidogenic or anti-infective effect of 2'-FL and LNnT.**

- **SA Health does not agree with the increased levels proposed by FSANZ of a maximum of 2.4 g/L for 2'-FL and LNnT. While these higher levels of 2'-FL and LNnT may be present in breast milk this application is regarding the addition of microbially produced 2'-FL and LNnT to infant formula, and these levels are not the levels used in the clinical trial presented by the applicant. Given there is no history of use of 2'-FL and LNnT in Australia and New Zealand in infant formula, safe levels should be based on this use not on the levels found in breast milk which is a more complex biofluid.**

- **SA Health strongly supports FSANZ's proposal not to permit the use of 'human milk-identical' or similar terms on infant formula or FSFYC labels. SA Health would additionally like to see the restriction of associated acronyms such as human milk oligosaccharide (HMO), HMO or HM-O on labels of infant formula or FSFYC. It has been noted that these terms are used overseas on infant formula and FSFYC labelling, these terms directly or indirectly infer that the use of 2'-FL or LNnT make the formula equivalent to breast milk, which is potentially misleading to the public.**

SA comments on FSANZ preliminary positions on regulatory measures in regard to the application from Glycom are as follows:

FSANZ summary position for addition to Infant formula products and FSFYC ie

- *Permit both 2'-FL and LNnT to be used as a nutritive substance, and as food produced using gene technology derived specifically from the GM production strains E.coli SCR6 (for 2'-FL) and E.coli MP572 (for LNnT), for use in infant formula products and FSFYC.*

SA Health response: Not supported.

Whilst the safety assessment for the addition of 2'-FL and LNnT appears acceptable, SA Health suggests application of the IFP Ministerial Policy Guideline - Specific Principle (j)

which requires there be '*a substantiated beneficial role in the normal growth and development of infants or children, or technical role'* combined with an '*appropriate level of evidence to link the physiological, biochemical and/or* ***functional*** *effects of the substance to specific health outcomes for infants, in infancy or childhood'*. FSANZ has stated that 2'-FL and LNnT have the '*potential to confer certain health outcomes in infants and young children*' and for 2'-FL '*the evidence supports a plausibility of an anti-infective health effect'*. These assessments, and the evidence presented to date, are not substantial enough to support the Specific Principle (j). SA Health is not satisfied that the applicant has provided *'appropriate evidence to link the physiological, biochemical and or functional effects of the substance to health benefits'*.

SA Health raises the following issues in relation to 'appropriate levels of evidence for a beneficial role':

- Bifidogenic effect
    - The majority of the evidence discussed by FSANZ to justify the possible bifidogenic effect of 2'-FL and LNnT comes from studies with breastfed infants. The Smith-Brown et al (2016) study measures bifidogenic activity in babies fed breastmilk from mothers of different secretor status and did not measure the content of these oligosaccharides in the breastmilk of participants. The study by Tannock (2013) investigates the faecal microbiotas of breastmilk fed infants with compared to groups fed infant formulas, one based on cows milk and the other on goats milk. The outcomes indicate a bifidogenic effect from breastmilk in comparison to the infant formula's but the levels of 2'-FL and LNnT of the breast milk or formula's were not measured. As the actual content of 2'-FL and LNnT are not measured in these studies it cannot be assumed that the benefits seen have a definite relationship to potential levels of 2'-FL or LNnT.
    - Of the four clinical studies in infants presented by the applicant only two were included in the FSANZ assessment as two were excluded. One study used a formula supplemented with LNnT only (Prieto 2005) and there was limited bacterial analysis. The study presented investigating 2'-FL and LNnT reported in the FSANZ assessment is only available for review in an abstract rather than a peer reviewed publication. Hence our ability to assess the quality of the study is limited. SA Health agrees with the conclusion in the abstract which states that 'further studies are warranted to evaluate whether such a shift in gut ecology towards the breastfed standard leads to health benefits' (Steenhout et al 2016).

- Anti-infective effect –
    - The main study presented by FSANZ justifying a potential anti-infective effect and the increased level of 2'-FL was a prospective study completed by Morrow et.al (2004) with Mexican participants followed from 1988 to 1991. This study found an inverse relationship between levels of 2'-FL and *Campylobacter jejuni* infections in breast fed infants. As previously highlighted breastmilk is a complex biofluid and while this study suggests a benefit associated with 2'-FL content in breastmilk it does not prove that adding this isolated oligosaccharide to infant formula will provide the same benefits.

Additionally, the authors discuss the need for research to determine if these simple milk oligosaccharides are providing this protection themselves of if they are a biomarker for a more complex mechanism and structures present in breastmilk (Morrow et.al 2004). Hence, while this study highlights a potential association of 2'-FL with an anti-infective effect for *C.jejuni* infections that is dose responsive it does not provide evidence that the addition of 2'-FL in isolation in infant formula will provide the same health benefits.

- Evidence was summarised from breastmilk studies and in vitro studies for the substances. FSANZ's assessment rated these as '*not demonstrated*' and '*possible in (specific) circumstances'*. This is consistent with the early stages of research into individual human milk oligosaccharides especially where it is recognised that there is a large diversity of human milk oligosaccharides and glycoproteins in milk that contribute to these anti-infective benefits in breast milk (Smilowitz et.al 2014).
- There is only one infant feeding trial presented to provide direct evidence of the benefits of the addition of 2'-FL and LNnT to infant formula (Puccio et al 2017) and FSANZ report this study provides '*limited evidence (of 2'-FL & LNnT) for reduced rates of parent-reported morbidity compared to supplemented formula. No associations with reduced rates of gastrointestinal illness were reported*'. In conclusion SA Health determines the evidence of a direct anti-infective effect of the combination of 2'-FL & LNnT added to infant formula is weak.

- There is very limited discussion and no clinical evidence presented to substantiate the addition of these substances to FSFYC specifically. The applicant suggests that the addition of these substances to toddler milk will ensure it more closely resembles breastmilk and note current intake levels in the US where permissions have been approved. However according to the *Policy Guideline on the intent of Part 2.9 – of the Food Standards Code- Special Purpose foods*- the composition of FSFYC should be consistent with their purpose which for children aged 1- <4 years is 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. The addition of 2'-FL and LNnT will not add to the nutritional composition of FSFYC as they are not digested. FSANZ's own assessment highlights that the addition *'may not strongly align with the intended purpose of these foods'.*

- If permission were to be granted for the voluntary addition of 2'-FL and LNnT to infant formula and/or FSFYC, SA Health notes that FSANZ has proposed 1) to only allow the prescribe ingredient names of '2-fucosyllactose' and 'Lacto-N-neotetraose' without the associated acronyms as the prescribed name for both infant formula and FSFYC labels, and 2) the term 'human milk- identical', or similar terms, would be prohibited for use on infant formula products in accordance with the existing requirements in in section 2.0.1-24.

- SA Health is aware that where some overseas countries have permitted the addition of 2'-FL and LNnT these formula products feature terms such as 'Human Milk Oligosaccharides', 'HMO' and HM-O prominently on the label. SA Health considers

the use of such wording on FSFYC products (which allow nutrient content and health claims) as undesirable and potentially misleading for the Australian public by creating the impression that these products are superior to other FSFYC products without these ingredients, or even equivalent to human breast milk. Furthermore, given the existence of line marketing of: infant formula ('Stage 1'), follow-on formula ('Stage 2') and toddler milk ('Stage 3') with similar packaging, the risk of cross promotion is increased (Berry et.al 2010), again inferring that their presence in FSFYC is beneficial and necessary, and encouraging the same conclusion amongst consumers for their infant formula counterpart. This kind of promotion would be inconsistent with the *IFP Policy Guideline*, which states that the labelling and advertising of infant formula products should not represent those products as an equivalent to, or better food, than breastmilk.

SA Health does not consider the evidence provided constitutes 'appropriate evidence' for the health benefits of a bifidogenic or anti-infective effect of 2'-FL and LNnT.

FSANZ's assessment determined that the applicants' **evidence did not** support the stated health effects associated with immune modulation, improved intestinal barrier function or alleviation of allergic responses. SA Health agrees there is insufficient evidence for these health effects.

Overall SA Health does not support development of a food regulatory measure to permit voluntary addition of 2'-FL and LNnT to infant formula and FDFYC.

FSANZ summary position:

- *Set a maximum permitted use level of 2.4 g/L for 2'-FL alone; and a total maximum level of 2.4 g/L for 2'-FL and LNnT combined with no more than 0.6 g/L of LNnT. For consistency with existing voluntary permissions for infant formula products and FSFYC, these levels will be expressed in mg/100 kJ and g/serving as follows:*
  Infant formula products:
  - *If only 2'-FL added – no more than 96 mg/100 kJ of 2'-FL*
  - *If both 2'-FL and LNnT added – no more than 24 mg/100 kJ of LNnT; and no more than 96 mg/100 kJ of 2'-FL and LNnT combined.*

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

- *and Prohibit the use of 2'-FL alone or with LNnT in combination with existing permissions for GOS and ITF for infant formula products and FSFYC (i.e. permissions for 2'-FL and LNnT would be used as alternatives to GOS and ITF).*

SA Health does not agree with the increased levels proposed by FSANZ of a maximum of 2.4 g/L for 2'-FL and LNnT.

The levels stated above do align with those approved for GOS. However, the literature states (Plaza-Diaz et al 2018) there is a lack of evidence to support a prescribed combination as suggested here. FSANZ state the above levels align with levels found in human milk and would be consistent with current FSANZ permissions on the use of GOS in infant formula. However, breast milk contains over 200 human milk oligosaccharides (Plaza-

Diaz et al 2018) and evidence suggests that prescribing the use of these ingredients in this way may be premature and not consider the possible interactive properties of combining further human milk oligosaccharides with these substances to consequently provide health benefits to infants (Plaza-Diaz et.al 2018). SA Health would also like to highlight that these levels are not the levels used in the clinical trial presented by the applicant. While these higher levels of 2'-FL and LNnT may be present in breast milk this application is regarding the addition of microbially produced 2'-FL and LNnT to infant formula where there is no history of use in Australian and New Zealand hence safe levels should be based on this use not on the levels found in breast milk which is a more complex biofluid. Additionally, the permissions for GOS were determined prior to introduction of the IFP Ministerial Policy Guideline. That is, before substantiated health benefits were considered in the approval process.

FSANZ summary position

- *Prescribe the ingredient names '2'-fucosyllactose' and 'Lacto-N-neotetraose' for infant formula products and FSFYC*.

If this application was to proceed in the future, SA Health agrees with the prescribed common names for the ingredients, as stated above. While FSANZ states that 'human milk-identical' or similar terms would be prohibited for use on infant formula products as per section 2.9.1-24, SA Health highlights the importance of ensuring there are no loop holes in the relevant standards that allow the use of these terms and abbreviations such as HMO or HM-O on both FSFYC and infant formula. Examples can be found internationally as shown below where the term HMO or HM-O is used extensively on the front of infant formula and FSFYC.

International Products and advertisements for Formula's containing human milk oligosaccharides

It is noted that some companies with GOS added to their formulas in Australia generally (but not exclusively) have “contains a prebiotic” on the front of the label. Therefore, it is highly likely that if this application is approved manufacturers would want to identify the addition of 2’-FL and LNnT on the front of infant formula and FSFYC in a similar way.

SA Health strongly supports FSANZ’s proposal not to permit the use of ‘human milk-identical’ or similar terms on infant formula or FSFYC. SA Health would additionally like to see the restriction of associated acronyms such as HMO or HM-O.

FSANZ summary position

- *Set specifications for 2'-FL and LNnT using the specifications provided by the applicant.*

SA Health has no further comment on these set specifications.

References

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