Application 1251 – 2'-FL combined with galacto-oligosaccharides and/or inulin-type fructans in infant formula products

1st call for submissions (CFS)

Summary

NSW appreciates the opportunity to comment on Application 1251 – 2'-FL (2'-fucosyllactose) combined with galacto-oligosaccharides (GOS) and/or inulin-type fructans (ITF) in infant formula products.

NSW would appreciate further investigation by FSANZ of any additional literature to support conclusions concerning safety and health benefit assessment provided in the 1st CFS. NSW appreciates the safety assessment conclusions in the 1st CFS are based on current ceilings in the Australia New Zealand Food Standards Code (the Code) for 2'FL and FOS/GOS. Given these estimates are based on Code ceilings, rather than likely levels of these ingredients in Infant Formula Products (IFP), it would seem prudent to explore IFP products containing 2'FL and FOS/GOS sold overseas by the applicant (Danone Nutricia). This would provide further assurance of safety given the limited literature and clinical evidence available on combining these 2 oligosaccharides. Similar concerns are raised concerning the availability of evidence relating to health benefit assessment, further exploration of the literature would be appreciated.

NSW further queries the nature of FOS/GOS as expressed in Standard 2.9.1 in the Code as they are not currently defined as nutritive substances or permitted novel foods. Given 2'FL is defined as a nutritive substance in the Code, it now appears pertinent to define the relationship between the functions of FOS/GOS and 2'FL in IFP, given Application 1251 suggests they are both added for purposes of simulating the oligosaccharide component of human milk in IFP.

NSW suggests this issue is considered as part of Proposal 1028 so there is regulatory clarity for all stakeholders on any future innovation concerning oligosaccharides intentionally added to IFP.

NSW acknowledges that the FSANZ Act (paragraph 16(2)(b)) permits FSANZ to make a standard that may relate to a particular brand of food, which enables the granting of exclusivity. Until 2020, exclusivity was used for novel foods following consideration of Proposal 305. Application 1155 saw FSANZ extend the use of exclusivity to nutritive substances 2'FL and Lacto-neotetraose (LnNT). NSW considers 2'FL and LnNT to be both novel foods and nutritive substances as Application 1155 was the first application to introduce these substances to IFP. Further applications concerning 2'FL admitted to the Code since A 1155 have been granted exclusivity as the 2'FL was derived from a novel source (a legitimate ground in Standard 1.5.1 for granting novelty).

NSW queries the basis of granting exclusivity for Application 1251. Application 1251 does not introduce anything new to the Code, both FOS/GOS have been added to IFP for many years and the 2'FL permission was granted exclusivity through Application 1190. Granting exclusivity on the basis of adding 2 existing substances in the Code is interpreting new ground on the application of this provision.

NSW is further concerned with the proposed drafting for Application 1251 in granting exclusivity. The current drafting suggests that ITF/GOS will be defined as a broad category, whereas 2'FL is defined as a specific substance from a specific source. The current drafting will effectively 'lock out' competitors to the applicants from innovating in the area of addition of 2'FL and other oligosaccharides additions. This is not the intent of exclusivity permissions as discussed in Proposal 305. NSW suggests a more specific combination of GOS/FOS be identified by the applicant should the exclusivity component of this application proceed. Based on the current drafting provided for Application 1251, NSW does not support exclusivity being provided to this application.

Further comments are provided on safety assessment, health benefit assessment and exclusivity.

Safety assessment

In its previous review of 2'FL and GOS/FOS as part of Application 1155, FSANZ prohibited the combination of 2'-FL with GOS and/or ITF due to a lack of evidence on infant tolerance to this combination. As this combination does not occur naturally in breastmilk at the levels proposed by the applicants, NSW supports FSANZ's approach to undertake pre-market safety assessment as part of Application 1251

NSW notes only one clinical study was supplied by the Applicant concerning infant formula containing a mixture of 2'FL and GOS/FOS. The findings of this study indicated that investigator reported adverse events (IRAE) were:

- 39.3% of the test group (fed IFP containing 8g/L FOS/GOS and 1g/L 2'FL),
- 31.7% of the control group (fed IFP without mixture of FOS/FOS and 2'FL).
- 24.6% of the breast-fed reference group (no IFP)

A 14.7% increase in IRAE compared to breast-fed infants and an 7.6% increase in IRAE compared to the control group fed IFP without 2'FL or FOS/GOS is observed. Whilst acknowledging the difference between the test and control groups were not statistically significant, it is an increase.

NSW requests FSANZ continue to search the literature to determine if further clinical trials are available for a 2'FL and GOS/FOS mixture.

NSW further suggests that review of international IFP supply could further assist in building the safety profile for 2'FL and GOS/FOS in IFP. An internet search revealed IFP containing GOS/FOS and 2'FL was available in Portugal, Germany, Romania, Belgium, UK, Austria, Thailand, Greece, Netherland, Italy, Ireland, Hong Kong, Poland, Spain, Slovakia, Czech Republic and Switzerland.

Some specific products:

- Aptamil Advanced First Infant milk (UK)

https://www.nutricia.co.uk/hcp/pim-products/aptamil-advanced-first-infant-milk-powder.html

This product contains GOS 4.8g/L, FOS 0.8/L, 2'-FL 1g/L

- Aptamil Profutura DUOADVANCE (German site)
https://www.aptaclub.de/en/products/milk-formula/aptamil-1-profutura-duo-anfangsnahrung.html

This product contains GOS 5g/L, FOS 0.8g/L, 2'-FL 1g/L

- Aptamil ESSENSIS Stage 1
https://www.apta.com.hk/zh-hk/our-products/essensis/essensis-1.html

This product contains GOS+lcFOS 8g/L, 2'-FL 1g/L

NSW further notes the levels of 2'FL and FOS/GOS in these products does not reach the ceiling permitted in the Code for 2'FL (2.4g/L). This is likely due to cost considerations associated with use of 2'FL in IFP. NSW suggests that FSANZ review the upper ceiling permitting in the Code for 2'FL to ensure it is associated with use of this substance alone, or in combination with other substances (e.g. GOS/FOS) so any further applications may be better informed by actual use levels rather than safety assessment ceilings placed into the Code.

Health benefit assessment

NSW notes no human intervention studies have been provided by the applicant to support the identified anti-pathogenic health benefit effect identified in previous FSANZ assessments of 2'FL. As this application is the first requesting the combination of GOS/FOS and 2'FL in IFP, NSW considers that some form of evidence of additional health benefit should be provided, especially as exclusivity is requested.

Neither GOS/FOS or 2'FL are novel substances for the purposes of this Application, the 2'FL source was assessed under A 1190 and the GOS/FOS assessed as part of Proposal 306 and Application 1055. In the absence of an additional health benefit identified for the combination of 2'FL and GOS/FOS, NSW questions whether FSANZ has given due regard to the Ministerial Policy Guideline for the Regulation of Infant Formula Products *policy principle j* .

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.

This principle requires the Authority to exercise caution where links are less clear. In its review of the health benefit assessment for this application, FSANZ notes *'conclusions could not be drawn on whether there are additional health benefits arising*

from supplementation with a combination of 2'FL and GOS and/or ITF compared to the individual components' (pg. 9, SD1 for Application 1251).

NSW requests further commentary on the combined health benefit of 2'FL and GOS/FOS from FSANZ, especially as exclusivity is sought by the applicant.

Exclusivity

Notwithstanding that the FSANZ Act (paragraph 16(2)(b)) enables the granting of exclusivity, it was through use of the proposal process (P305 *Permission for exclusivity of use of novel foods*) that debate and clarity about its use was provided for novel foods in 2007. The principal driver for this work was to provide a suitable reward to industry applicants for their research and development investment as the transparent FSANZ process potentially dis-advantages applicants through the public consultation process. Succinctly, applicants are forced to publicly disclose significant details relating to their investment at cost, to their competitors benefit. The exclusivity proposal was prepared as part of the review of the novel food standard, which was requested of FSANZ by Food Ministers. This request is supported by the Ministerial Council Policy Guidelines on Novel Foods. One of the higher order principles in this document is to encourage fair trade. This concept is discussed in detail in the Final Assessment Report for Proposal 305 (pg. 6, Section 4.2, Final Assessment Report Proposal 305).

Until 2020, exclusivity was perceived to be confined to novel food. FSANZ extended its use to nutritive substances in its consideration of A1155. In NSW's view, A1251 is potentially extending the application of exclusivity again.

NSW is concerned about the application of exclusivity to Application 1251 on several grounds:

- The nature of exclusivity sought for in Application 1251 does not appear 'novel'. There are existing permissions in the Code for GOS (Proposal 306), FOS (Application 1055) and 2'FL sourced from genetically modified *Escherichia coli* BL21 strains (Application 1190). Exclusivity was granted to Application 1190 on the basis that the production method to supply 2'FL was novel to the Code. NSW does not understand the 'novel' aspect of combining existing permissions in the Code (especially when one has already been granted exclusivity).
- GOS/FOS are not nutritive substances or novel foods according to Standard 2.9.1 of the Code. 2'FL sourced from genetically modified *Escherichia coli* BL21 strain has already been granted exclusivity (Application 1190). NSW does not understand how exclusivity may be granted to a substance that is not either a novel food or nutritive substance according to the Code.
- The permission proposed in the Code for exclusivity for an '*inulin-type fructan, a galacto-oligosaccharide or both'* manufactured by Nutricia Australia Pty Ltd is not limited to a specific oligosaccharide combination. It could be interpreted as applying to any combination of relevant substances within that broad category. The drafting as written could be interpreted as limiting any industry innovation in the family of substances known as 'inulin-type fructans' or 'galacto-oligosaccharides' to one company. NSW considers this is not the intent of exclusivity as discussed in Proposal 305 or intended in the Ministerial Policy Guideline for Novel Foods.

For the reasons suggested above, NSW does not support the granting of exclusivity proposed for Application 1251.

As it seems from A1251 that FSANZ will consider exclusivity beyond novel food or nutritive substances, NSW encourages FSANZ to provide a stronger framework than that presently available in the public domain to allow broad stakeholder engagement, debate and understanding of the breadth of its potential use by the standards setter.

ENDS

The views expressed in this submission may or may not accord with those of other NSW Government agencies. The NSW Food Authority has a policy which encourages the full range of NSW agency views to be submitted during the standards development stages before final assessment. Other relevant NSW Government agencies are aware of and agree with this policy.