**Dietitians Association of Australia**

**Response to FSANZ on Application A1055**

**Short Chain Fructo-oligosaccharides**

**February 2013**

The Dietitians Association of Australia (DAA) is the national association of the dietetic profession with over 5000 members, and branches in each state and territory. DAA is a leader in nutrition and advocates for better food, better health, and better living for all.


Contact Person: [redacted]
Position: Senior Professional Services Dietitian
Organisation: Dietitians Association of Australia
Address: 1/8 Phipps Close, Deakin ACT 2600
[redacted]


The DAA understands the application A1055 is to amend the *Food Standards Code* (the Code) to:

1) permit the optional addition of short chain fructo-oligosaccharides derived from sucrose by enzymatic action (short chain $FOS_{sucrose}$) to Infant Formula Products (Standard 2.9.1), Foods for Infants (Standard 2.9.2) and Formulated Supplementary Foods for Young Children (Standard 2.9.3 Division 4).

2) modification of Standard 1.3.3 to permit the use of a new microbial source of invertase (EC 3.2.1.26) enzyme from a strain of the fungus *Aspergillus niger* as a processing aid (enzyme). This enzyme is to be used in the production of short chain FOS.

We do not support the addition of $scFOS_{sucrose}$ to infant formula products (2.9.1) on the basis of the inadequacies of the risk assessment provided and the vulnerable nature of this population.

Despite the lack of evidence and a thorough assessment of $scFOS_{sucrose}$, these are unlikely to form a significant proportion of the diet in young children or the general population (due to the varied nature of eating patterns). There are no clear grounds for preventing the addition of $scFOS_{sucrose}$ to foods for young children and to the general food supply. As such we support the addition of $scFOS_{sucrose}$ to these foods. However, consideration should be given to clearly labelling $scFOS_{sucrose}$ added to these foods to ensure that consumers who are sensitive to fructose and fructooligosaccharides can easily identify and avoid these foods.

**Infant Formula (Standard 2.9.1)**

The DAA does not support the amendment to Standard 2.9.1 for the following reasons:

1. FSANZ's Risk and technical assessment concludes that short chain $FOS_{sucrose}$ produced by invertase-catalysed condensation of sucrose is as safe as inulin derived substances (IDS) already permitted to be added to infant formula products, foods for infants and formulated supplementary foods for young children. However there is evidence to suggest $FOS_{inulin}$ and $FOS_{sucrose}$ should not be assumed as one in the same without a thorough risk assessment:

   The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) committee reviewed published scientific data on probiotic and prebiotic formulas for healthy infants and found that the clinical effects and safety of one prebiotic product should not be extrapolated to other prebiotics. $ScFOS_{sucrose}$ exclusively comprise very short chain lengths unlike $scFOS_{inulin}$ and IDS which consist of a variety of chain lengths. The literature suggests that the physiological effects of FOS depend on their chain lengths. Studies and clinical practice have found that decreasing chain lengths of FOS result in greater gastrointestinal symptoms such as bloating, diarrhoea, pain and flatulence.[1,2]

   Therefore it cannot be assumed that adding the maximum 3g/L of only very short chain $scFOS_{sucrose}$ will have the same effect as 3g/L of a mixture of long and short chain FOS. FSANZ considered that the physiological equivalence of $scFOS_{sucrose}$ was established by one in vitro study that found comparable levels of short chain fatty acids and gas. Given infants are a vulnerable population who have immature systems and a complete reliance on infant formula as a sole or predominant source of nutrition it is imperative that safety assessments of changes to infant formulae are comprehensive and that the benefits of these changes are clear.

   Therefore, it cannot be assumed $FOS_{sucrose}$ is as safe as $FOS_{inulin}$ already permitted to be added to infant formula[3].

2. Research on FODMAPS suggests fructans with a lower degree of polymerisation are more likely to be malabsorbed by adults. Although the research is in adults, given the immaturity of the infant gut means we should ensure a higher degree of scrutiny when considering fructans such as $FOS_{sucrose}$ for infants[4].

   $FOS_{sucrose}$ has a different degree of polymerisation DP (2-4) to $FOS_{inulin}$ DP (2-9). The DP may impact on the rate of fermentation and osmotic load in the gut, however this has not been investigated in the risk assessment.

3. The studies provided by the applicant are not sufficient for a risk assessment:
   a. The studies are unpublished and have not been subject to peer review.
   b. A summary of results is presented but there is limited discussion of methodology or limitations in order to make an assessment of the quality of the studies.

c. The studies are smaller and shorter than recommended by the FDA guidelines on clinical studies in infants[5].

Infancy is a unique period that requires unique safety measures. Most organ systems are not fully developed at birth, and are highly susceptible to environmental inputs as they undergo further development. The assessment of safety requires studies that have sufficient subject numbers to detect subtle changes in growth and development (as noted by ICHSAG) and are of sufficient duration to capture any delayed effects. The Institute of Medicine of the National Academies, Committee on the Evaluation of the Addition of Ingredients New to Infant Formula (2004)[6] indicate that 120 day studies are insufficient and the duration of growth studies should cover at least the period when infant formulas remain a substantial source of nutrients in the infant diet. The risk assessment of $scFOS_{sucrose}$ fell well short of that expected for a new ingredient being added to infant formula.

- All of the studies provided by FSANZ were less than 4 months duration with the exception of two: one of these was in older infants and young children and so cannot be extrapolated to infants less than 6 months of age, and the other tested an unspecified concentration and type of FOS in young infants and thus provides no information on the specific effects of $scFOS_{sucrose.}$
- Seven of the ten studies presented in the assessment of the physiological effects of scFOS in infants and young children are unpublished and non peer reviewed. Importantly, the full details of these studies were not available for analysis.
- A 2004 paper prepared for EFSA on the Safety and suitability for particular nutrional use by infants of fructooligosacchardies in infant and follow on formulae was dismissive of the 2 key published studies relied on in this application[7].
- The studies presented do not specify whether the scFOS used was $scFOS_{sucrose}$ (which consists of very short chain lengths) or scFOS derived from inulin (which has a greater variation in chain length). As such the safety and tolerance of $scFOS_{sucrose}$ cannot be established.
- Many of the studies did not assess adverse effects or tolerability of the tested formula and the vast majority did not have sufficient subject numbers or duration to adequately detect these.
- There was no assessment of fussiness/colic/crying behaviour in infants. Only one unpublished study mentioned fussiness but only included older children (aged 2-5 years). Given a member of the ICHSAG group (during the assessment of p306: Additon of Inulin/FOS and GOS to Food) stated that the evidence suggests that a significant potential adverse effect of scFOS would be crying behaviour and colic, it is imperative that this effect be determined or ruled out.
- The assessment of the risk of dehydration in infants fed $scFOS_{sucrose}$ was not sufficient to rule this adverse effect out completely. Only one of the 4 studies that assessed dehydration used an objective measure of hydration status and this study was unpublished. FSANZ states that $scFOS_{sucrose}$is not expected to behave any differently to the variety of human milk oligosaccharides in the digestive tract and as such dehydration is unlikely. Given different oligosaccharides can have various

physiological effects and that human milk does not contain any FOS[8] this statement does not support the notion that dehydration will not occur with $scFOS_{sucrose}$.

4. In the FSANZ Proposal *P306 the addition of FOS and GOS,* a member of the ICHSAG noted the evidence suggests a significant potential adverse effect of $FOS_{sucrose}$ would be crying behaviour and colic. There has been no assessment of the effect of $FOS_{sucrose}$ on crying behaviour or colic in the application[9].

5. In consideration of the benefit that $scFOS_{sucrose}$ will have for infants, a potential stool softening effect to move the stool of formula-fed infants closer to those of breastfed infants was suggested. ICHSAG noted that the majority of studies listed (those that were unpublished and provided by the Applicant) provided inconsistent evidence that $scFOS_{sucrose}$ up to 3g/L increased stool frequency or had a stool-softening effect. Only 2 published studies provided any support for a benefit: Bettler and Euler (2006) and Euler (2005). The report states that Bettler and Euler (2006) found a significant reduction in the incidence of constipation in the 3g/L scFOS group. What was not included was the explanatory comment by the authors that stated that "this comparison was not significant for events of constipation considered by the principal investigator to be formula related." The review of this paper by EFSA (2004) also stated that the statement of a lower rate of constipation could not be adequately substantiated. We note there was also increased vomiting in the group receiving 1.5g/L which was also deemed not to be formula related.

   The Euler (2005) study found a stool softening effect after 1 week, however this does not provide sufficient information to determine whether this was a transient or sustained effect. Furthermore despite FSANZ reporting there were no apparent adverse effects of giving FOS in this study, the study actually does report an increase in adverse events with increasing concentrations of FOS up to 3g/L compared with infants receiving human milk. It is reported that 97% of infants in the 3g/L group experienced adverse effects compared with 59% in the human milk group. An excessive number of 11 stools a day was the maximum number of daily stools observed with 3g/L of FOS. The study also reported that satisfaction ratings for formula acceptability declined after the FOS began and were lower for the 3g/L FOS group than the 1.5g/L.

   In the discussion on the stool softening effect there is also no discussion of the increased incidence of watery or loose bowel motions found in many of the studies. FSANZ dismiss this by stating that ICHSAG agreed that the descriptor "watery" is not equivalent to diarrhoea, with no acknowledgement that watery or loose stools are not a desirable outcome.

   On the basis of the data provided by FSANZ, we do not agree with FSANZ's conclusion that $scFOS_{sucrose}$ up to 3g/L has the potential beneficial effect of softening stools and reducing constipation.

**Future Research**

The DAA considers that the supplementation of formula with probiotics and/or prebiotics is an important field of further research.

In the future, validated clinical outcome measures assessing the effects of probiotic and/or prebiotic supplementation of formulae should be used in well-designed and carefully conducted RCT, with relevant inclusion/exclusion criteria and adequate sample sizes. Such trials should also define the optimal doses and intake durations, as well as the safety of the probiotics and prebiotics.

Because most of the trials were company funded, independent trials, preferentially financed jointly by national/governmental/ European Union bodies and international organisations, would be desirable[3].

**Foods for Infants (Standard 2.9.2) and Formulated Supplementary Foods for Young Children (Standard 2.9.3 Division 4)**

The DAA supports the amendment that relates to Foods for Infants (2.9.2) and Formulated Supplementary Foods for Young Children (2.9.3 Division 4) on the basis that no public health and safety risk occurs as a result.

**References**


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