Comments from the Victorian Departments of Health and Primary Industries, and Dairy Food Safety Victoria

Due date: 11 February 2013

The Victorian Departments of Health, Primary Industries, and Dairy Food Safety Victoria welcome the opportunity to comment on Application A1055. The Application seeks permission to change the Australian and New Zealand Food Standards Code (the Code) to allow the addition of short chain fructooligosaccharides (scFOS) derived from sucrose ($scFOS_{sucrose}$) to infant formula products (IFP) for young children, and foods in the general food supply through changes to the following Standards:

- amend Standard 1.1.1 to allow the voluntary addition of $scFOS_{sucrose}$ to general foods through a revision of the current definition in the Code for inulin derived substances (IDS);
- amend Standard 1.3.3 to extend the current permission for the processing aid invertase to be obtained from a new microbial source, i.e. *Aspergillus niger*, to produce $scFOS_{sucrose}$;
- amend Standard 2.9.1 to permit the voluntary addition of $scFOS_{sucrose}$ to infant formula (for infants up to 6 months), and follow-on formula (for infants from 6 months to 12 months); and
- amend Standard 2.9.2 and 2.9.3 Division 4 to permit the voluntary addition of $scFOS_{sucrose}$ to infant foods and formulated supplementary foods for young children (for infants over 6 months and for toddlers over 12 months).

Summarised below are the principal issues that we would like to raise:

1. Based on the risk assessment provided we do not support the addition of $scFOS_{sucrose}$ to IFP without further work to allay reservations regarding the risk assessment methodology and evidence base for the proposal. Infants are the most vulnerable group in the population that the Code seeks to protect. It is therefore appropriate that regulatory considerations for the addition of new substances to IFPs are underpinned by both rigorous risk assessment methodologies and quality evidence, and align with the policy guidelines on IFP.
2. We support the addition of $scFOS_{sucrose}$ to foods for young children. This is because this group of children consume a mixed diet from a variety of sources. Hence, the intake of $scFOS_{sucrose}$ should contribute only a small component, if any, of their total food intake.
3. We support the addition of $scFOS_{sucrose}$ to the general food supply despite a concern for a risk to a sub-set of the population with functional gastrointestinal disorder (FGID). Individuals with FGID have a low tolerance for fructose and FOS, particularly $scFOS_{sucrose}$ that consists of only very short chain FOS. To manage this risk we recommend that clear food labelling identify the presence of this substance in food to better inform individuals affected by the disorder.
4. On the basis of the evidence provided, we are satisfied that the processing aid invertase, and its source *A. niger,* are safe and suitable for the production of $scFOS_{sucrose}$.

Issues:

1. **The risk assessment has not adequately differentiated between $scFOS_{sucrose}$ and IDS leading to an underestimate of potential health risks**

The assessment of the Application assumed a chemical and physiological equivalence between IDS and $scFOS_{sucrose}$. It is clearly stated in the Assessment Report that the risk and technical assessments viewed $scFOS_{sucrose}$ as a substitute for the (already permitted) IDS in the Code. This key assumption has compromised the ensuing approach to the risk and technical assessment as the focus is more broadly on IDS rather than specifically on $scFOS_{sucrose}$.

The definition for IDS in the Code collectively refers to inulin, long chain inulin, and FOS including scFOS. This definition incorporates scFOS derived from inulin ($scFOS_{inulin}$), but specifically excludes short chain FOS derived from sucrose. The Code currently allows the addition of IDS to infant formula products up to a maximum of 3g/L.

Inulin and FOS, including $scFOS_{inulin}$ and $scFOS_{sucrose}$ are closely chemically related carbohydrates that differ in the degree of chain polymerisation (DP); the larger the DP the longer the chain length. Inulin is characterised by a DP of greater than 10, while FOS is characterised by a DP of less than 10. $ScFOS_{inulin}$ are short chain FOS with a DP of 2-9. $ScFOS_{sucrose}$ are also short chain FOS but with a DP of exclusively 2-4: that is, carbohydrates of very short chain lengths. We maintain that this chemical structure differs sufficiently to warrant individual assessment.

The Applicant is seeking permission to allow the maximum of 3g/L to be exclusively made up of very short chain FOS. Our concerns centre on the documented, differing physiological effects of consuming oligosaccharides of varying chain lengths. All inulin and most of scFOS escape digestion in the small intestine and are largely broken down in the large intestine[1]. The literature reports that FOS of different chain lengths appear to exert different physiological effects. Abdominal symptoms such as increased flatulence, bloating, diarrhoea and abdominal pain have been found to increase with consumption of shorter chain lengths of FOS in studies and in clinical practice [2] [3]. FOS are highly fermentable and some scFOS can be digested in the small intestine causing an increase in the osmotic load, which is associated with greater gastrointestinal symptoms[4]. Additionally, secondary small bowel motility changes are also cited with scFOS[5] and a higher osmotic load[6] which may be of relevance to infants,

[1] Shepherd SJ & Gibson PR. (2010). Evidence-Based dietary management of functional gastrointestinal symptoms: The FODMAP approach, *Journal of Gastroenterology and Hepatology*, 25: 252-258.
[2] Rumessen JJ & Gudmand-Heyer E. (1998). Fructans of chicory: intestinal transport and fermentation of different chain lengths and relation to fructose and sorbitol malabsorption, *American Journal of Clinical Nutrition*, 68: 357-64.
[3] Shepherd SJ & Gibson PR. (2006). Fructose Malabsorption and Symptoms of Irritable Bowel Syndrome: Guidelines for Effective Dietary Management, *J Am Diet Assoc*, 106:1631-1639.
[4] Barret & Gibson 2007 Clinical Ramifications of Malabsorption of Fructose and Other Short-chain Carbohydrates, *Practical Gastroenterology*, 29 (8): 51-65.
[5] Shepherd SJ & Gibson PR. (2010). Evidence-based dietary management of functional gastrointestinal symptoms: The FODMAP approach, *Journal of Gastroenterology and Hepatology*, 25: 252-258.

particularly in understanding the risks related to colic and crying behaviours of infants. Therefore, the clinical outcomes for $scFOS_{sucrose}$ may be substantially different to IDS, presenting differing levels of health and safety risks.

2. There are concerns with the risk and technical assessment methodology and process undertaken in regard to the development and analysis of the evidence base, and with the resulting conclusions.

A sound risk assessment and rigorous evidence base are warranted for any consideration to amend the Code. This is particularly important when a proposed change to IFP is raised. Infants' organs, including the gastrointestinal system, are immature and are susceptible to external inputs as they develop. As IFP provides the sole or predominant source of nutrition for infants it has the potential to significantly impact on development. Consequently, IFP require assessments that are based on scientifically valid data.

The collection and analysis of the body of evidence for this proposal is of concern. In particular, we have concerns regarding the quality of the studies that underpin the risk assessment process for $scFOS_{sucrose}$ for infants and adults.

A comprehensive systematic review of the evidence has not been presented. The review of the literature on FOS is incomplete as the terms and search engines used to guide the literature review were limited. In particular, the studies regarding the identification of all possible risks associated with $scFOS_{sucrose}$ have not been discussed in the body of evidence presented in the Application. This has deleteriously impacted the assessments and conclusions that have been drawn in the Application regarding risks of $scFOS_{sucrose}$.

Our concerns regarding the evidence that has been relied upon for the risk and technical assessment include:

(i) Questionable studies in the body of evidence

- seven of the ten studies presented in the assessment of the physiological effects of scFOS in infants and young children are unpublished works and therefore not been peer reviewed. We are also unable to access the full details of these studies and must rely on FSANZ's summaries.
- the same two randomised controlled studies that the European Food Safety Authority (EFSA) rejected in 2004 are relied on as key studies in the body of evidence.
- the studies described in the Application paper which assess scFOS do not specify whether the scFOS assessed was $scFOS_{sucrose}$ or scFOS derived from inulin or scFOS from any other source.
- one piece of evidence presented was a survey with methodological issues. It did not define many of the key concepts including the substance studied. This

[6] Seidl H, Schmidt T, Gundling F, Pfeiffer A. (2013). The effect of osmolarity and caloric load on small bowel motility, *Neurogastroenterol Motil*., 25 (1): 11-16.

would suggest that this evidence is of poor scientific quality and should have been excluded from consideration.

(ii) Methodological limitations of studies:

- *Purpose of the study*: a number of the studies were conducted by the manufacturer for the purpose of hazard identification (to assess toxicity) of scFOS and were not designed to evaluate benefits. For example, measures of stool consistency and frequency were not reported in the study so constipation was used as the surrogate for these measures.
- *Sample size*: a number of the studies involved small participant numbers. These provide low statistical power and are inadequate to detect differences in interventions, for example when comparing a group of infants fed formula with added scFOS versus those fed formula without added scFOS. This means important effects such as changes in growth or tolerance might not be detected. This issue was also highlighted by the Infant and Child Health Scientific Advisory Group (ICHSAG), a FSANZ expert advisory group.
- *Duration of study:* a number of the studies were of very short treatment duration (i.e. one week or one month). This is inconsistent with US guidelines that recommend that clinical studies should be of at least three to four months duration to adequately monitor growth to ensure safety and demonstrate benefits[7].
- *Lack of appropriate control group:* a number of the studies do not compare results with a breast fed control group. This is also inconsistent with recommendations from the EU for the assessment of suitability of substances added to IFP[8].
- *Lack of definition of key concepts:* a number of the studies had definitional issues, e.g. no definition for constipation and stool consistency, (such as what was defined as loose stools), making it difficult to assess benefits of consumption.

3. The same weak evidence base has also informed the assessment of benefit of $scFOS_{sucrose}$.

The Application report states that a benefit to infants who consume $scFOS_{sucrose}$ potentially exists. The statement '$scFOS_{sucrose}$ *has the potential to* soften infant stools and *may* reduce the incidence of constipation' incorporates a certain degree of uncertainty but also implies a notion of possibility. However, the problematic weak evidence base in this instance is more heavily weighted towards uncertainty.

The FSANZ ICHSAG is an expert group that is consulted on regulatory issues regarding the Code and the health and safety of infants and children. We note that in its assessment of the potential benefit of $scFOS_{sucrose}$ the ICHSAG

[7] Food and Drug Administration, http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/InfantFormula/ucm170649.htm

[8] Koletzko B, Ashwell M, Beck B, Bronner A, and Mathioudakis B. (2002). Characterisation of Infant Food Modifications in the European Union; *Ann Nutr Metab,* 46: 31–242.

dismissed all of the unpublished studies in light of the inconsistent evidence of a beneficial effect on stools.

We have concerns with the conclusions presented by FSANZ on the two remaining published studies that allegedly supported the theory of a benefit (refer: Bettler and Euler 2006[9] and Euler *et al* 2005[10]). FSANZ indicates that Bettler and Euler (2006) found a significant reduction in constipation in the group receiving 3g/L of scFOS, supporting their suggestion of a benefit. However the original paper states that "this was not significant for events of constipation considered by the principal investigator to be formula related", which appears to clarify that the change in constipation was not related to the formula. Similarly they state that the increase in vomiting seen with the group receiving 1.5g/L of scFOS was not related to the formula.

The study by Euler *et a*l (2005) did report a significant change in stool consistency during the one week trial period. However we are of the view that the period of study is not sufficient to verify a sustained effect. This study also reported a significant increase in adverse effects with increasing levels of scFOS up to 3g/L and decreasing scores of satisfaction with the formula, as rated by carers.

In 2004, the EFSA[11] examined both of these studies and found no evidence of benefits to infants from the addition of FOS to infant formula at the equivalent level of 3.0g/L. More recent evidence presented in the current Application is not sufficiently strong to countervail this finding due to methodological flaws and inconsistent findings.

4. Insufficient and questionable evidence strength has been used to address the risk regarding dehydration in infants.

There are four studies in the Application report to counter the concern regarding the risk of dehydration to infants that was raised by EFSA in 2004[12]. However, amongst the four studies, the unpublished paper by Impeokparia and Lasekan[13] is the only study that used an objective method for the evaluation of dehydration.

[9] Bettler J and Euler AR. (2006). An evaluation of the growth of term infants fed formula supplemented with fructo-oligosaccharide, *International Journal of Probiotics and Prebiotics*, 1(1): 19-26.

[10] Euler AR, Mitchell DK, Kline R and Pickering LK. (2005). Prebiotic effect of fructooligosaccharide supplemented term infant formula at two concentrations compared with unsupplemented formula and human milk. *Journal of Paediatric Gastroenterology,* 40: 157-164.

[11] EFSA. (2004). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the safety and suitability for particular nutritional use by infants of fructooligosacharides in infant formulae and follow-on formulae, *EFSA Journal,* 31: 1-11.

[12] EFSA. (2004). Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the safety and suitability for particular nutritional use by infants of fructooligosacharides in infant formulae and follow-on formulae, *EFSA Journal,* 31: 1-11.

13 Imeokparia M and Lasekan JB. (2009). Comparative gastrointestinal tolerance of various infant formulas in health term infants. Study No. AK54. Abbottt Nutrition, Abbottt Laboratories, Research and Development and Scientific Affairs. Unpublished.

The other three studies use the more subjective clinical observation to assess level of hydration. Although the objective measure study was a randomised trial, it is inconsistent with the EU and US recommendations for clinical studies for the assessment for infant formula[14] [15]. These recommendations state that the study period should be of at least three to four month duration to identify adverse risks and that a breast-fed control group should be used as a comparison to adequately assess the effects on infant growth and development. The Impeokparia and Lasekan study does not meet these design requirements. Therefore, it is our view that placing reliance on one study that is of lesser quality cannot be regarded as sufficient to discount the risk for dehydration.

5. The risk assessment process is incomplete

As discussed above, we have concerns that the risk assessment is incomplete and lacks identification of the range of possible adverse effects to infants and adults. Specifically omitted are the potential adverse effects of crying behaviours and colic for infants, and for adults an exacerbation of the gastrointestinal symptoms in people with FGID.

During the previous assessment of P306 it was noted by a member of the ICHSAG group that evidence suggests that a significant potential adverse effect of scFOS would be crying behaviour and colic. These behavioural effects may be in response to direct or secondary gastrointestinal symptoms associated with scFOS and quite possibly accentuated by $scFOS_{sucrose}$ (as discussed earlier under point 1 above). While gastrointestinal related effects may not necessarily affect growth and development, they are significant and unnecessarily distressing to the infants and their carers with potentially serious consequences, and therefore warrant further investigation.

FGID is a specific gastrointestinal disorder commonly referred to broadly as irritable bowel syndrome (IBS). It is associated with symptoms of wind, bloating, constipation and/or diarrhoea and abdominal pain. FGID is known to affect up to 15% of the general population and is managed through dietary manipulation involving the restriction of all fermentable carbohydrates. IDS, i.e. short and long chain FOS and inulin, are all therefore required to be minimised in the diet. As discussed above, the literature suggests that scFOS of shorter chain lengths have the potential to contribute to more pronounced gastrointestinal symptoms[16.] Therefore $scFOS_{sucrose}$ appears to pose a risk to the sub-population of adults with FGID. This is a risk that should be acknowledged, assessed and managed through an appropriate risk management strategy including clearer labelling to inform individuals at risk.

[14]Food and Drug Administration, http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/InfantFormula/ucm170649.htm.

[15] Scientific Committee on Food (2003). Report of the Scientific Committee on Food on the Revision of Essential Requirements of Infant Formulae and Follow-on Formulae SCF/CS/NUT/IF/65, http://ec.europa.eu/food/fs/sc/scf/out199_en.pdf.

[16] Shepherd SJ & Gibson PR. (2006). Fructose Malabsorption and Symptoms of Irritable Bowel Syndrome: Guidelines for Effective Dietary Management, *J Am Diet Assoc.*, 106:1631-1639

6. There is no FOS in breastmilk

Although there are a number of oligosaccharides in human breast milk they primarily consist of Galactooligosaccharides (GOS); there is no FOS or scFOS or $scFOS_{sucrose}$ in breast milk[17]. The policy guidelines stipulate that breastmilk should be a primary reference for the composition of infant formula.

7. The EU permits only small quantities of FOS in infant formula and follow-on formula due to the lack of adequacy of supporting evidence.

The EU permits the addition of a total maximum of 8 g/L of FOS and GOS to infant formulae and individually in a combination in which their content cannot exceed 10% and 90% respectively. This means that the regulations allow only a maximum of 0.8 g/L of FOS that can be added to infant formula. Other combinations and maximum levels of FOS and GOS may also be used in the EU. However, this is conditional on scientifically demonstrating the suitability of the change in terms of the expected benefits and safety to infants.

A revision of the 0.8 g/L maximum to allow a higher quantity of FOS to be permitted in infant formula was considered by EFSA in 2004 but was subsequently rejected. The EFSA reviewed data from two studies and found no evidence of benefits to infants from the addition of FOS to infant formula at 1.5g/L or 3.0g/L. Instead the EFSA found reasons for safety concerns that related to loose stools and increased risk of dehydration[18]. Infant formula containing FOS, specifically $scFOS_{sucrose}$, does not appear to be available in the EU market.

FSANZ is proposing to permit the addition of approximately 3g/L of $scFOS_{sucrose}$ infant formula and follow-on formula. This quantity of FOS is more than three times the current allowable maximum in the EU. FSANZ has accepted the same two randomised controlled studies that EFSA rejected in 2004 for inclusion in its body of evidence to support this Application.

Conclusion

Infant formula is the sole food source for infants for up to 6 months of age and remains the predominant source until 12 months. Infants have less developed organs including the gastrointestinal system. Infants are consequently the most vulnerable population group whose health and safety the Code is designed to protect. It is therefore imperative that risk assessments for IFPs are underpinned by a thorough risk assessment approach and rigorous evidence to demonstrate safety and benefit to infants. This will ensure that all risks are identified,

[17] Huisman M, van Beusekom CM, Lanting CI, Nijeboer HJ, Muskiet FA and Boersma ER. (1996) Triglycerides, fatty acids, sterols, mono- and disaccharides and sugar alcohols in human milk and current types of infant formula milk. *Eur J Clin Nutr*. 50(4): 255-60.

[18] EFSA (2004) Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the safety and suitability for particular nutritional use by infants of fructooligosacharides in infant formulae and follow-on formulae, *EFSA Journal,* 31: 1-11.

analysed and managed appropriately as needed. The Application as it stands does not contain sufficient information to support the benefits of the proposed addition, nor the lack of risk to this vulnerable population.

Response to questions posed by FSANZ:

Q.1 Are there other costs or benefits that should be considered in the impact analysis?

This is dependent on the outcomes from the further work suggested.

Q.2. Are there other parties you think the proposed variation to the relevant Standards may affect?

We recommend contacting research experts who have a working knowledge in this area such as Sue Shepherd (Dietician), and Prof Peter Gibson (Medicine and Gastroenterology), Box Hill Hospital.

Q.3. Does the proposed terminology and definition provide appropriate clarity and consistency?

The proposed terminology and definition provided are a great improvement on those used in P306 and do provide clarity and consistency. The assumption that $scFOS_{sucrose}$ and IDS are equivalent is not supported however.