Department of Health and Human Services Tasmania

Comments on Application A1055 Short Chain Fructo-oligosaccharides

February 2013

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The Department of Health and Human Services Tasmania appreciates the opportunity to comment on FSANZ assessment of an application by GTC Nutrition to amend the *Australia New Zealand Food Standards Code* (the Code) to permit the optional addition of short chain fructo-oligosaccharides produced from sucrose by enzymatic action ($scFOS_{sucrose}$) 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).

The main issues the Department wishes to raise are:

- Equivalence of $scFOS_{sucrose}$ to FOS_{inulin}
- Physiological effect of $scFOS_{sucrose}$
- Quality of the studies

The Department has no comment on the invertase *A.Niger* or impact of $scFOS_{sucrose}$ in food for infant, formulated supplementary foods for young children or the general food supply. The absence of any acute toxicological hazard means there is less concern with the addition of $scFOS_{sucrose}$ to these foods. The following comments relate specifically to infant formula where the target audience may consume infant formula as their sole source of nutrition.

$scFOS_{sucrose}$ is equivalent to FOS_{inulin}

The Department has concerns with the one of the key assumptions underlying the risk assessment which considers $scFOS_{sucrose}$ equivalent to short chain short chain fructo-oligosaccharides produced enzymatically by degrading inulin (FOS_{inulin}) for use in infant formula.

The internationally recognised specification for short chain FOS states the Degree of Polymerisation (DP) of the mixture varies between 2-9 for inulin derived short chain fructo-oligosaccharides and 2-4 for sucrose derived short chain fructo-oligosaccharides(Food Chemicals Codex 2012)

Whether the degree of polymerisation results in different physiological properties has not been examined as part of the risk assessment as the FOS_{inulin} and $scFOS_{sucrose}$ were considered 'nature identical'.

The chemical bonds are identical and no distinction is made between $scFOS_{sucrose}$ and FOS_{inulin} with regard to their chemical properties, or methods of analysis. However while they have overlapping chemical structures, evidence that the physiological effects are the same has not been presented.

The assessment states that there is no *a priori* reason to anticipate any unique physiological effects of $scFOS_{sucrose}$ within the gastrointestinal tract of infants and young children.

The ESPGHAN committee on nutrition reviewed available scientific data on probiotic- and prebiotic-supplemented formula to healthy infants. ESPGHAN did not have safety concerns with regard to growth and adverse effects of currently permitted substances. However they noted that the safety and clinical effects of one product should not be extrapolated to other products (Braegger, Chmielewska et al. 2011).

The Department is not aware of any permitted use of $scFOS_{sucrose}$ in infant formula in the European Union. While *'other combinations and maximum levels of oligosaccharides and galacto-oligosaccharides may be used in accordance with article 5, which requires the suitability of an ingredient for a particular nutritional use by infants to be established by generally accepted scientific data'* no evidence has been presented that $scFOS_{sucrose}$ is permitted in the European Union.

The results of the small number of variable quality studies presented do not support the assumption that they are equivalent. Studies with FOS_{inulin} found reduced constipation (Bettler and Euler 2006) and more frequent bowel movements and softer stools (Euler, Mitchell et al. 2005); studies with short chain $FOS_{sucrose}$ do not have consistent results:

- (Malacaman, Choudhry et al. 1993) found no significant difference (small size)
- (Pickering, Hofer et al. 1993) found significantly softer stools for the $scFOS_{sucrose}$ group on day 28 but not 56 or 84
- (Merritt, Williams et al. 2005) found higher incidence of watery stool in $FOS_{sucrose}$ groups (2 and 3.0 g/L) days 1-14 higher incidence watery stools $FOS_{sucrose}$ group (3 g/L) day 15-28 (small size)
- (Imeokparia and Lasekan 2009) found no significant difference.

Other studies do not specify the nature of the substance referred to (Yamamoto and Yonekubo 1993).

Physiological impacts of FOS

The model of large bowel fermentation using three healthy adult male volunteers showed little difference with the gas production between $scFOS_{sucrose}$ and FOS_{inulin} except "*gas production was somewhat slower from the fermentation of inulin"* and the rate of production was unable to be compared because the FOS_{inulin} did not follow a logistic model.

FOS are one of a group of short chain carbohydrates (Fermentable Oligo-, Di- and Mono-saccharides And Polyols or FODMAPs) implicated in functional gut disturbances in up to 15% of the population (Shepherd and Gibson 2006; Barrett and Gisbson 2007). Data is not available for infants.

However, a retrospective review of breath hydrogen test (BHT) results found the majority (88.2%) of infants referred with gastrointestinal symptoms had fructose malabsorption. And the odds of

testing positive for fructose malabsorption decreased with age. The authors suggest that the low threshold for fructose absorption in infants has significant implications infants with gastrointestinal symptoms consuming fructose (Jones, Burt et al. 2011).

The high osmotic activity and rapid fermentability of FOS may contribute to luminal distension bloating, abdominal discomfort, and motility changes (Shepherd and Gibson 2006; Barrett and Gisbson 2007).

> *"fructans with a low degree of polymerization have a greater osmotic effect and are more rapidly fermented than those with a high degree of polymerization, the chain length of fructans may be an important determinant of the degree of contribution to symptoms"(Shepherd and Gibson 2006).*

Whether this has clinical implications for infant formula has not been demonstrated. However mixing short- and long-chain oligosaccharides attenuated short-chain oligosaccharide fermentation rate and extent (Hernot, Boileau et al. 2009). Given the highly fermentable nature of fructans and FOS generally this may be an important consideration especially of the tolerance in the infant digestive system.

> *It has been shown that prebiotic properties are likely to be influenced by the monosaccharide composition, the glycosidic linkage between the monosaccharide residues, and the DP of the prebiotic (Hernot, Boileau et al. 2009).*

Imprecise definition of prebiotic and fructo-oligosachharide terminology in the literature makes comparison difficult and the inconsistent results are also problematic. Where the substance is specified as galacto-oligosaccharide (GOS) with or without FOS_{inulin} with the results appear to be more consistent

> *Prebiotics in formula did increase weight gain but had no impact on length or head circumference gain. Prebiotics increased stool frequency but had no impact on stool consistency, the incidence of colic, spitting up / regurgitation, crying, restlessness or vomiting. There was no impact of prebiotics on the volume of formula tolerated, infections and gastrointestinal microflora. The quality of evidence was compromised by imprecision, inconsistency of results, use of different study preparations and publication bias (Mugambi, Musekiwa et al. 2012).*

$scFOS_{sucrose}$ may be as safe as Inulin Derived Substances (IDS) already permitted, but the evidence presented to confirm this is unclear. In fact, the risk assessment relies on evidence of inulin derived substances to support the use of $scFOS_{sucrose}$.

It is estimated that infantile colic causes 10–20% of early paediatrician visits, in addition to parental stress. A systematic review was conducted to examine the impact of dietary change for infantile colic. The review found weak evidence that removal of poorly digested carbohydrates (high levels of free fructose) from the infant's diet has promise, but additional clinical studies are required to make a recommendation (Iacovou, Ralston et al. 2012).

The Infant and Child Health Scientific Advisory Group (ICHSAG) reported that scFOS up to 3.0 g/L is unlikely to cause adverse events or gastrointestinal intolerance (spit up/vomiting, flatulence, diarrhoea, burping, and fussiness). However they commented that the level of confidence in the data was questionable due to the small size of the studies. Ideally there should be at least 30-35 infants/sex/group to have sufficient power to detect subtle changes.

Gastrointestinal symptoms other than spit-up or vomiting were not reported in the risk assessment. Potential gastrointestinal symptoms could theoretically relate to the rapid fermentation and high osmotic load placed on immature gut.

In 2008 a member of the ICHSAG noted in response to *Proposal P306 the addition of Inulin/FOS and GOS to food* that addition of FOS could result in gastrointestinal symptoms in infants (Food Standards Australia New Zealand 2008). There has been no assessment of the effect of $scFOS_{sucrose}$ in regard to gastrointestinal symptoms such as flatulence, cramping, crying or colic in the application.

The risk assessment concludes that $scFOS_{sucrose}$ is expected to undergo the same degradation as IDS and HMOs in the infant digestive tract. This conclusion is not supported by the evidence presented.

Quality of the evidence presented

The studies provided by the applicant are unpublished and have not been subject to peer review. 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. It is noted that the study by Malacman et al (1993) presented conflicting results in the microbiological assessment and was not considered further, but is presented as one of the primary references to support the physiological effect of infant formula with $FOS_{sucrose}$, which found no difference between intervention and control groups . The number of infants in this trial is likely to be too small to detect any significant difference in adverse effects or treatment failures, spit ups or vomits and intolerance to the formula between treatment arms.

Merritt et al (2005) found softer stools in the supplemented $FOS_{sucrose}$ groups and noted adverse events were comparable among groups. The number of infants in this trial is likely to be too small to detect any significant difference in adverse effects or treatment failures, spit ups or vomits and intolerance to the formula between treatment arms.

Imeokparia and Lasekan (2009) found no difference in stool frequency , consistency or adverse events over 4 weeks

The US Food and Drug Agency guidelines on Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants recommend:

- weight gain be determined over an interval of 3 to 4 months
- each arm of a trial needs 28 subjects of a specified sex to detect a significant difference in weight gain. If both sexes are studied, it will be necessary to take into account the sex-related difference in rate of gain.
- 'tolerance' studies generally report fussiness, colic, cramps, regurgitation, and stool characteristics (FDA 1988).

The risk assessment notes that there were no adverse effects in infants and young children that consumed infant formula containing scFOS. The studies presented report a selected range of tolerance and undefined 'adverse effects'. The key concern with this assessment is the quality of the studies presented. Small studies do not have sufficient power to detect significant differences in stool characteristics or importantly rates of withdrawal particularly due to intolerance. Studies of short duration (<3months) are unlikely to detect any significant difference in growth rates. The small

short term studies on short chain $FOS_{sucrose}$ preclude making an assessment about whether withdrawal rates because of lack of tolerance are of significance.

In 2004 the European Food safety Authority found:

> *Under the described conditions of use, fructooligosaccharides added to infant formula showed variable effects on consistency and frequency of stools. There was an increased prevalence of adverse effects, including loose stools, in infants fed formula with added fructooligosaccharides. As no measures were made to demonstrate satisfactory water balance, the possibility of increased risk of dehydration can not be excluded, raising concerns with respect to the safety of such formulae. The Panel concludes that there is no evidence of benefits to infants from the addition of fructooligosaccharides to infant formula at the conditions specified by the manufacturer while there are reasons for safety concerns.(EFSA Panel on Dietetic Products Nutrition and Allergies 2004)*

The risk assessment does not consider the safety of short chain $FOS_{sucrose}$ per se so the statement that "*short chain $FOS_{sucrose}$ is as safe as IDS"* (Inulin Derived Substances) has not been substantiated for infants. The potential stool softening effect has not been evaluated against the potential intolerance, increased crying, colic as these measures were not reported in the tolerance trials.

In conclusion the Department has significant concerns with the risk assessment which assumes that $scFOS_{sucrose}$ has the same physiological impact as FOS_{inulin}. The potential physiological impacts associated with the lower degree of polymerisation of $scFOS_{sucrose}$, including increased gastrointestinal symptoms, crying behaviour, and colic have not been investigated. The small size and short term nature of the studies presented are unlikely to have the power to detect subtle differences in growth or other outcomes. In the absence of more robust evidence a cautious approach should be taken to protect infants and their carers from potential adverse impacts in the absence of a demonstrated benefit.

Barrett, J. and P. Gisbson (2007). "Clinical Ramifications of Malabsorption of Fructose and Other Short-chain Carbohydrates." Practical Gastroenterology **August**(51-65).

Bettler, J. and A. Euler (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.

Braegger, C., A. Chmielewska, et al. (2011). "Supplementation of infant formula with probiotics and/or prebiotics: a systematic review and comment by the ESPGHAN committee on nutrition." J Pediatr Gastroenterol Nutr. **52**(2): 238-250.

EFSA Panel on Dietetic Products Nutrition and Allergies (2004). "Opinion of the Scientific Panel on Dietetic products, nutrition and allergies [NDA] related to the safety and suitability for particular nutritional use by infants of fructooligosaccharides in infant formulae and follow-on formulae " EFSA Journal **31**(1-11).

Euler, A., D. Mitchell, et al. (2005). "Prebiotic effect of fructo-oligosaccharide supplemented term infant formula at two concentrations compared with unsupplemented formula and human milk." Journal of Paediatric Gastroenterology **40**: 157-164.

FDA. (1988). "Clinical Testing of Infant Formulas With Respect to Nutritional Suitability for Term Infants." Food Retrieved Jan 31, 2013, from http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/InfantFormula/ucm170649.htm.

Food Chemicals Codex (2012). http://online.foodchemicalscodex.org/online/pub/index?fcc=8ands=0andoYr=2012andoMo=6andoDa=1

Food Standards Australia New Zealand (2008) "Addition of Inulin / FOS & GOS to Food ".

Hernot, D., T. Boileau, et al. (2009). "In vitro fermentation profiles, gas production rates, and microbiota modulation as affected by certain fructans, galactooligosaccharides, and polydextrose." J Agric Food Chem. **57**(4): 1354-1361.

Iacovou, M., R. Ralston, et al. (2012). "Dietary Management of Infantile Colic: A Systematic Review." Maternal And Child Health Journal **16**(6): 1319-1331.

Imeokparia, M. and J. Lasekan (2009). Comparative gastrointestinal tolerance of various infant formulas in health term infants. Study No. AK54. . A. N. A. L. R. a. D. a. S. Affairs. **Unpublished**.

Jones, H. F., E. Burt, et al. (2011). "Effect of Age on Fructose Malabsorption in Children Presenting With Gastrointestinal Symptoms." Journal of Pediatric Gastroenterology and Nutrition **52**(5): 581-584 510.1097/MPG.1090b1013e3181fd1315.

Malacaman, E., I. Choudhry, et al. (1993). The effect of an alternate carbohydrate on stool characteristics and tolerance in healthy, term infants. Study No. CPAE04. Ross Laboratories Abbott laboratories Paediatric Nutrition Research and Development Department. **Unpublished.**

Merritt, R., T. Williams, et al. (2005). Effect of non-digestible carbohydrate on the fecal flora of term infants. Study No. AK16. . Ross Products Division Abbott Laboratories. Columbus, OH, USA. **Unpublished.**

Mugambi, M., A. Musekiwa, et al. (2012). "Synbiotics, probiotics or prebiotics in infant formula for full term infants: a systematic review." Nutrition Journal

11(1): 81.

Pickering, L., J. Hofer, et al. (1993). The effect of an alternate carbohydrate on growth of healthy, term infants. Study No. CP-AE12a,b,c. Ross Products Division Abbott laboratories Pediatric Nutrition Research and Development Department. **Unpublished**.

Shepherd, S. J. and P. R. Gibson (2006). "Fructose malabsorption and symptoms of irritable bowel syndrome: guidelines for effective dietary management." Journal of the American Dietetic Association **106**(10): 1631-1639.

Yamamoto, Y. and A. Yonekubo (1993). "A survey of physical growth, nutrition intake, fecal properties

and morbidity of infants as related to feeding methods." Journal of Child Health **52**(4): 465-475.