Queensland Government

Queensland **Health**

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Standards Management Officer
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Dear Sir / Madam

Submission – Application A1055 – Short Chain Fructo-oligosaccharides

Thank you for the opportunity to provide a submission on the Call for Submissions for Application A1055.

This submission provides technical advice and comments related to this issue. It was prepared with the advice of officers from other relevant Queensland Government agencies. The submission does not represent a Queensland Government position, which will be a matter for the Queensland Government when notification is made by the FSANZ Board to the Legislative and Governance Forum on Food Regulation.

The Application seeks permission to change the Australia New Zealand Food Standards Code (the Code) to allow the addition of short chain fructo-oligosaccharides derived from sucrose ($scFOS_{sucrose}$) to infant formula products (IFP), foods for infants, formulated supplementary food for young children (FSFYC), and foods in the general food supply.

The focus of the following comments relate to infant formula products. Infants are the most vulnerable group in the population who may consume infant formula as their sole source of nutrition. No comment is provided on the invertase produced by *Aspergillus niger* nor on the impact of $scFOS_{sucrose}$ in foods for infants, formulated supplementary foods for young children or the general food supply. As no acute toxicological hazard was identified there is less concern with the addition of $scFOS_{sucrose}$ to these foods.

Equivalence of $scFOS_{sucrose}$ and $scFOS_{inulin}$

The current permissions in the Code allow the addition of inulin-derived substances (IDS) to infant formula products up to a maximum of 3g/L, up to a maximum of 0.8 g/100 g for food for infants and up to a maximum of 1.6 g/serve for FSFYC.

The definition of inulin-derived substances (IDS) in the Code incorporates short chain FOS derived from inulin ($scFOS_{inulin}$) but not $scFOS_{sucrose}$.

The internationally-recognised specification for scFOS states that the degree of polymerisation (DP) of the mixture varies between 2 to 9 $scFOS_{inulin}$ and 2 to 4 for $scFOS_{sucrose}$ (Food Chemicals Codex 2012). No distinctions are made between $scFOS_{sucrose}$ and $scFOS_{inulin}$ with regard to their properties, technological function, methods of analysis or impurity levels.

Underpinning the risk assessment is the assumption that $scFOS_{sucrose}$ which is synthesised enzymatically from sucrose is physiologically equivalent to $scFOS_{inulin}$ which is produced by the enzymatic degradation of inulin. The assessment states that scFOS is currently excluded from infant formula products, infant foods and FSFYC based solely on its mode of synthesis. There is no discussion relating to whether the DP results in different physiological properties.

The risk assessment considers that $scFOS_{sucrose}$ will be degraded like IDS and human milk oligosaccharides (HMOs) in the infant digestive tract and no changes in digestion is expected in infants or young children consuming products containing $scFOS_{sucrose}$.

Physiological effects of scFOS in infants and young children

The assessment report states 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 study of Hernot et al (2009) is quoted as support for this.

However this *in vitro* study used a model of large bowel fermentation derived from three health adult male volunteers. The risk assessment states that the study showed little difference between $scFOS_{sucrose}$, $scFOS_{inulin}$, inulin and galacto-oligosaccharides (GOS) with regard to the production of gas and short chained fatty acids (SCFAs) or any effect on bacterial flora. However gas production was somewhat slower from the fermentation of inulin.

In terms of potential physiological benefits for infants the results of studies presented do not support the assumption that $scFOS_{sucrose}$ and $scFOS_{inulin}$ are equivalent.

Two published studies with $scFOS_{inulin}$ found softer stools (Euler et al. 2005) and reduced constipation (Bettler and Euler 2006). However the unpublished studies using short chain $FOS_{sucrose}$ did not show consistent results. This conclusion was also reached by the FSANZ Infant and Child Health Scientific Advisory Group (ICHSAG).

The relevant studies and summary findings are as follows:

- Pickering, Hofer and Zielger (1993) found significantly softer stools for the $scFOS_{sucrose}$ group on day 28 but not day 56 or 84.
- Malacaman et al. (1993) found no significant difference between groups consuming formula with 0, 1.5g/L and 3.0g/L $scFOS_{sucrose}$. These groups were small.
- Merrit, Williams and Price (2005) found a significantly higher incidence of watery stools in the 2.0 and 3.0g/L $FOS_{sucrose}$ groups over study days 1-14 and significantly higher incidence of watery stools for the 3.0g/L $FOS_{sucrose}$ group over study days 15-28. However the published version of this study (Xia et al. 2012) which concentrated on studying the bacterial populations of the groups reported that '*the formula feeding groups did not differ in stool consistency and stool frequency or frequency of spit-up or vomit during the entire study'.*
- Imeokparia and Lasekan (2009) found no significant difference between groups. This study used a soy-based formula rather than a whey-based formula.

The other relevant study on infants was a published survey but it is not clear what substance was tested (Yamamoto and Yonekubo 1993).

Potential of scFOS to cause adverse physiological effects

It is considered that the assessment of adverse effects has not been fully addressed.

Short chain FOS are rapidly fermented in the gut. The high osmotic load and rapid gas production may lead to luminal distension, bloating, abdominal discomfort, and motility changes (Shepherd and Gibson 2006; Barrett and Gibson 2007). A lower degree of polymerisation is associated with more rapid fermentation and a higher osmotic load. Therefore *'the chain length of fructans may be an important determinant of the degree of contribution to symptoms*' (Shepherd and Gibson, 2006).

In the study by Hernot et al. (2009) short-chain oligosaccharides were more rapidly fermented and produced more short chain fatty acids and gas than those with greater degrees of polymerization. Mixing of short- and long-chain oligosaccharides attenuated the rate and degree of fermentation of short-chain oligosaccharides.

It is important to examine the possible clinical implications of these findings for infants consuming infant formula containing $scFOS_{sucrose}$.

The main symptoms of gastrointestinal intolerance reported in the summaries for the infant formula trials using $scFOS_{sucrose}$ were spit-up and vomiting. Where adverse effects were reported these were not defined. There are other potential gastrointestinal symptoms that could theoretically relate to the rapid fermentation and high osmotic load placed on an immature gut.

During the assessment *of Proposal P306 Addition of Inulin / FOS & GOS to Food* in 2008 a member of the ICHSAG noted that the evidence suggested that a significant potential adverse effect of scFOS would be crying behaviour and colic. These types of symptoms also have impacts on carers. There has been no assessment of the effect of $scFOS_{sucrose}$ in this regard in the application.

Strength of evidence presented

The studies used for the risk assessment have many limitations and do not provide convincing evidence that short chain $FOS_{sucrose}$ is as safe as IDS.

The studies on $scFOS_{sucrose}$ provided are unpublished and therefore not subject to peer review. Only a summary is provided and little discussion is included about the methodology and other aspects which impact on the quality of the studies. The studies presented a selected range of tolerance effects, did not define adverse effects or detail reasons for withdrawals from the studies.

A key concern is that some of the studies involved numbers of infants that were likely to be too small to detect any significant differences between treatment groups. Also many of the studies were of short duration so that important effects such as changes in gastrointestinal tolerance and growth might not be detected.

The study by Malacaman et al. (1993) found no significant difference between control and treatment groups over 29 days. Merrit, Williams and Price (2005) found softer stools in the supplemented $FOS_{sucrose}$ groups and noted adverse events were comparable among groups although this was not confirmed in the published version of the study (Xia, Williams et al. 2012). The study was over 28 days. Imeokparia and Lasekan (2009) found no difference in growth, stool frequency, consistency or adverse events over 4 weeks. This study used a soy-based formula rather than a whey-based formula. ISCHAG members queried whether observations in infants consuming soy-based formula containing scFOS could be extrapolated to other types of formulas (e.g. whey-based).

In all these studies the number of infants 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 groups.

Both issues of study participant numbers and duration of studies were highlighted by ICHSAG. They commented that ideally there should be at least 30-35 infants/sex/group to have sufficient power to detect subtle changes.

The US Food and Drug Agency guidelines on Clinical Testing of Infant Formulas with Respect to Nutritional Suitability for Term Infants (FDA 1988) recommend that:

- 'tolerance' studies should pay particular attention to reports of fussiness, colic, cramps, regurgitation, and stool characteristics.
- determination of 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.

Considerable weight has been given to the two studies using $scFOS_{inulin}$ (Euler et al. 2005; Bettler and Euler 2006) to support the use of $scFOS_{sucrose}$. If anything these studies highlight uncertainly around the safety of scFOS.

ISHCAG discussed the limitations of these studies noting that in the study by Bettler and Euler (2006) there was no evidence that there had been any systematic analysis of adverse events and no information on how stool consistency/constipation had been assessed.

These two studies were originally submitted unpublished to the European Food Safety Authority (EFSA) in a dossier by Wyeth. The EFSA Panel on Dietetic Products Nutrition and Allergies was requested to assess the safety and suitability of fructo-oligosaccharides for use in infant formulae and follow-on formulae.

The Panel (EFSA 2004) in assessing the studies concluded:
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.

History of use

Fructo-oligosaccharides and galacto-oligosaccharides may be added to infant formula and follow on formula in the European Union. The content of these substances should not exceed 0.8 g/100 mL in *a combination of 90% oligogalactosyl-lactose and 10% high molecular weight oligofructosylsaccharose*. Other combinations and maximum levels of fructo-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 acceptable scientific data.

However, there does not appear to be any permitted use of $scFOS_{sucrose}$ in infant formula in the European Union.

As already discussed the safety and suitability of $scFOS_{inulin}$ was assessed by the EFSA and 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.*'

Summary

The risk assessment concluded that:

- $scFOS_{sucrose}$ is expected to undergo the same degradation as IDS and HMOs in the infant digestive tract. However there has been no assessment of the potential adverse physiological impacts of $scFOS_{sucrose.}$ such as crying or colic.

- that the consumption of scFOS in infant formula in amounts up to 3.0 g/L is unlikely to cause adverse effects in healthy infants. However, this is based on studies with small participant groups and of short duration and which are therefore unlikely to have the statistical power to detect significant differences in gastrointestinal tolerance and growth.

- That $scFOS_{sucrose}$ in infant formula has the potential to soften stools and may reduce constipation. However the results were not consistent across the relevant studies.

This submission has focussed on infants. However it is noted that there are only a small number of studies on young children and that consequently conclusions about the safety of scFOS for young children have been extrapolated from the conclusions about the safety for infants. Therefore the concerns raised in this submission about the risk assessment for infants also raises questions about the risk assessment for young children.

Conclusion

Concern is expressed that the evidence as presented in the risk assessment is insufficient in terms of its quality and breadth. The safety and benefits to infants of consuming formula with $scFOS_{sucrose}$ has not been adequately established. It is considered that further work needs to be undertaken to address these issues.

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