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 fructooligosaccharides in infant formulae and follow-on formulae

(Request N° EFSA-Q-2003-020)

(adopted on 19 February 2004)

SUMMARY

The request to assess the safety and suitability for particular nutritional use by infants of fructooligosaccharides in infant formulae and follow-on formulae has been evaluated by the Panel on the basis of data submitted and from the literature.

Data submitted included the reports on two studies: 1) a growth study in healthy infants fed with an infant formula supplemented with 1.5 or 3.0 g/L fructooligosaccharides; 2) a study of the faecal microbiota in healthy infants fed with an infant formula supplemented with 1.5 or 3.0 g/L fructooligosaccharides.

The data submitted indicate:

1. In the growth study, the anthropometric data suggest that the use of infant formula supplemented with either 1.5 or 3.0 g/L of fructooligosaccharides results in a normal growth pattern in healthy term infants less than two weeks of age for periods of up to twelve weeks. Serum markers of protein and mineral status and kidney function were also in the normal range.

2. No effect of fructooligosaccharides in rendering the faecal microbiota more similar to that in human milk-fed infants was demonstrated in infants fed an infant formula supplemented with either 1.5 or 3.0 g/L of fructooligosaccharides for one week.

3. 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.

As no data have been submitted nor were available from the literature on the use of fructooligosaccharides in follow-on formula, the Panel is not in the position to evaluate the safety and suitability of FOS for such use.

KEY WORDS

Infant formula, follow-on formula, infant nutrition, fructooligosaccharides, oligofructosyl-saccharose, oligofructose, prebiotic, faecal microbiota, bifidobacteria.

BACKGROUND

During its review of the essential composition of infant formulae and follow-on formulae the European Commission received a request for the review of fructooligosaccharides (FOS) for use under conditions different from those specified by the Scientific Committee on Food (SCF) in December 2001.

The European Union legislation specifies certain compositional criteria in Directive 91/321/EC on infant formulae and follow-on formulae. There are no specific criteria for FOS in the existing legislation, however, the general provision that ingredients must be suitable for the particular nutritional use by infants from birth applies. In addition, infant formulae and follow-on formulae shall not contain any substance in such a quantity as to endanger the health of infants and young children. The SCF had no major concerns on the inclusion of up to 8 g/L of a combination of 90% galactooligosaccharides (GOS) and 10% FOS (i.e. 0.8 g/L of FOS) to infant formulae and follow-on formulae (SCF, 2001a and 2001b). These statements were further confirmed in the SCF Report on Essential Requirements of Infant Formulae and Follow-on Formulae (SCF, 2003).

TERMS OF REFERENCE

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission requests the European Food Safety Authority to issue a scientific opinion on the safety and the suitability for particular nutritional use by infants of fructooligosaccharides (FOS) at the conditions specified by the manufacturer in infant formulae and follow-on formulae.

ASSESSMENT

1. Nature of oligosaccharides

Oligosaccharides contain a small number (3-10) of monosaccharide residues connected by glycosidic linkages (IUPAC-IUBMB Joint Commission on Biochemical Nomenclature, 1982). Human milk contains more than 130 different oligosaccharides (Kunz *et al.*, 2000) that were recently shown to be resistant to enzymatic digestion in the gastrointestinal tract (Engfer *et al.*, 2000).

Human milk oligosaccharides may be used as substrates for colonic fermentation and induce an increase in the number of bifidobacteria in the colonic microbiota of breast-fed infants, associated with a decrease in the number of potentially pathogenic bacteria (Kunz *et al.*, 2000).

A bifidus-dominated microbiota may be beneficial for infants, leading to protection against enteric infections. However, an increase in the faecal bifidobacteria level cannot be considered a health benefit *per se*. Even if breast-feeding tends to contribute to higher levels of bifidobacteria in the faecal microbiota, the differences seem to be less pronounced with modern infant formulae than in the past (Harmsen *et al.*, 2000). Since it is not possible to add human milk oligosaccharides to infant formulae and follow-on formulae, other oligosaccharides have been added to infant formulae and follow-on formulae.

Oligofructosyl-saccharose (oligofructose; fructooligosaccharides, FOS) and oligogalactosyl-lactose (oligogalactose; galactooligosaccharides, GOS) have been used in infant formulae and follow-on formulae in Europe and in Japan (Gibson and Roberfroid, 1995). Oligofructose is produced from chicory roots by partial enzymatic hydrolysis and contains one molecule of saccharose to which 1 to more than 60 fructose molecules are added. Oligofructose is not found in human milk.

Typical commercial preparations of FOS contain a high proportion of oligossacharide, e.g. Raftilose® 95 contains ≥93.2% oligofructose and <6.8% glucose + fructose + sucrose.

2. Study of the effect of an infant formula with FOS on growth

Study description: A prospective, controlled, randomised multicentre study was undertaken in healthy, term infants appropriate for gestational age by 17 investigators in the USA, in order to compare the efficacy with respect to growth parameters, the acceptability and the tolerance of regular S-26® bovine milk-based formula (Control formula) with S-26 formula supplemented with FOS at 1.5 (Low FOS formula) and 3.0 g/L (High FOS formula), respectively, during a period of 12 weeks. The origin of FOS was not stated. FOS was added to the S-26 formula, the carbohydrate content of which was not diminished. Measurements of blood urea nitrogen and of serum levels of albumin, calcium, magnesium, phosphorus, creatinine, triglycerides, low-density lipoproteins and cholesterol performed at baseline and after 12 weeks served as additional parameters for the assessment of nutritional safety. After written informed consent had been obtained from a parent or legal guardian, a baseline visit, medical history and physical examination, including measurement of weight, length, and head circumference, had been performed, infants were randomised within 3 days to receive either of the three formulae. Telephone follow-up was done at weeks 2, 6, and 10. At weeks 4, 8, and 12, physical and anthropometric examination was repeated.

Study results: Of the 297 infants who entered the study, 98 received the Control formula, 98 received the Low FOS formula, and 101 received the High FOS formula. The mean gestational age was similar among the formula groups. Baseline values for age, weight, length, and head circumference were not significantly different among the 3 feeding groups.

Two hundred twelve infants completed the study, including 66 infants in the Control group (67%), 72 infants in the Low FOS group (74%), and 74 infants in the High FOS group (73%). The most frequent reasons for discontinuation were physician/family request (18%), adverse events (4%), and failure to return (4%).

Over the 12-week study period, the average weight gain for all infants was ≥9 g/kg/day. In the population which completed the study, there was a statistically significant difference in length

and in the length-for-age percentiles at Week 8 (higher in infants fed Control formula). By Week 12, the differences were no longer significant.

For weight-for-length, there was a statistically significant difference between the two FOS supplemented formula groups at Week 12 (higher in the Low FOS Formula group; p=0.0356). The differences between the formula groups in head circumference-for-age percentiles did not reach the level of statistical significance.

The anthropometric results of the study suggest that all three formulae are equally effective in promoting growth over the 12-week study period. When compared to the CDC reference ranges, using percentiles and Z scores, the study infants grew appropriately. At the end of the study, none of the infants had low weight-for-age Z scores, one infant had a low length-for-age Z score, and eight infants had low weight-for-length Z scores, including five infants in the High FOS group (6.8%), two infants in the Control group (3.0%), and one infant (1.4%) in the Low FOS group.

Approximately 89% of the infants experienced at least one adverse event during the study. Fifty-five per cent of infants experienced adverse events that were considered by the investigator as formula-related. No explanation is given as to how the investigators defined an adverse event as being formula-related. Moreover, no precise definitions were given for the main adverse events, such as constipation, diarrhoea, loose stools, spitting up, and vomiting. According to the files of the dossier related to adverse events, the investigators used a range of terms to define symptoms and adverse events. The most common gastrointestinal adverse events (affecting at least 10% of infants) were flatulence, constipation, spitting up, vomiting and diarrhoea. There was no difference between the three study groups.

The study formula was permanently discontinued because of an adverse event in 18 infants in the Control group, 14 infants in the Low FOS group, and 17 infants in the High FOS group. Sixteen infants experienced a total of 29 severe adverse events, including six infants in the Low FOS group and five infants each in the Control group and the High FOS group. Of the 16 infants, 13 infants completed the study, two infants discontinued because of physician/family request, and one infant discontinued the study because of the adverse events (reflux and dyspnea). The most common serious adverse events were bronchiolitis (n=5), viral infection (n=4), and fever (n=3). One infant experienced gastroenteritis and one infant experienced diarrhoea, fever, vomiting, oliguria, and dehydration, both needing hospitalization. No infant death was reported in the study.

The serum markers of protein and mineral status and kidney function did not show any statistically significant differences among the formula groups at completion of the study. For all groups, the mean values for these measures remained within the normal ranges.

Summary and comment: The gain in weight, length, and head circumference was satisfactory during the study. Even if a statistically significant difference was found in length and in length-for-age percentile between the Control group and the High FOS group at Week 8, it was not clinically relevant (difference of length of 0.9 cm between the 2 groups, the Control group being the longer) and was not found at the end of the study. Although a difference of weight for length percentile was found at Week 12 between the two FOS supplemented formula groups, the percentile values remained within the normal ranges, at 61.6 and 51.1, respectively

The information available in the studies of formulae containing a 10% FOS - 90% GOS mixture at a concentration of 4, 8, or 10 g/L shows a normal growth (weight, length and head circumference) in preterm and term infants (Boehm *et al.*, 2002; Moro *et al.*, 2002; Schmelzle *et al.*, 2003). However, since the FOS supplementation is different in the present study (1.5 or 3.0 g/L of FOS) and in the FOS-GOS studies (0.4 to 1 g/L of FOS), no comparison can be made.

From this multicentre growth study, it can be assumed that growth of infants fed infant formula supplemented with 1.5 or 3.0 g/L was satisfactory on a short-term basis (12 weeks). However, contrary to what is advocated, there was no comparison to a reference group or to a database of breast-fed infants for the same period of time (12 weeks) (SCF, 2003; ESPGHAN, 2001; Koletzko, 2002).

The data submitted do not allow an assessment of the acceptability and tolerance of the two infant formula supplemented with 1.5 or 3.0 g/L of FOS, because of a lack of clear definitions of the main adverse events related to the use of FOS. Although it is stated in the dossier that infants receiving the High FOS formula had a lower rate of constipation, this statement is not adequately substantiated.

The analysis of recognised serum markers of protein and mineral status and kidney function showed no significant difference among the formula groups at the end of the study. For all groups, the mean values for these parameters remained within the normal ranges.

3. Study of the effect of an infant formula with FOS on the faecal microbiota

Study description: A controlled, prospective, randomised, crossover, outpatient, single-site study of at least five weeks duration was undertaken in healthy term infants appropriate for gestational age and 2 to 6 weeks of age. Five groups of infants were fed either 1) Human milk exclusively throughout the study period of 5 weeks; 2) Experimental formula 1 (with 1.5 g/L FOS) during Week 2 and Control formula for the other 4 weeks; 3) Experimental formula 1 (with 1.5 g/L FOS) during Week 4 and Control formula for the other 4 weeks; 4) Experimental formula 2 (with 3.0 g/L FOS) during Week 2 and Control formula for the other 4 weeks; 5) Experimental formula 2 (with 3.0 g/L FOS) during Week 4 and Control formula for the other 4 weeks. Control and Experimental formula differed only in FOS content.

The primary objective was to determine which dose of FOS was 1) associated with bifidogenic faecal microbiota changes, and 2) resulted in faecal microbiota closer to the microbiota of human milk-fed infants. The secondary objective was to determine which dose of FOS was 1) associated with decreased *Enterococcus*, *Bacteroides*, and *Clostridium* counts, and *Clostridium difficile* toxin-positive stools, and 2) resulted in the incidence of *Clostridium difficile* toxin-positive stools similar to the incidence in human milk-fed infants. Thirdly the dose of FOS was to be determined which was associated with continuing bifidogenic microbiota changes and a lower incidence of *Clostridium difficile* toxin-positive stools at 7 days post-termination of FOS feeding. Safety assessment was to compare the tolerance and acceptability of the two FOS formulae.

Infants delivered by caesarean section or treated with antibiotics and antifungal medications or, in the exclusively human milk-fed group, infants from mothers treated with antibiotics, were excluded.

Infants were weighed and examined once a week. A stool sample was collected immediately prior to each visit. Stool specimens were taken to the study site and processed within 24 hours of collection. Anaerobic and aerobic organisms were counted at the genus level on selective media: bifidobacteria, lactobacilli, enterococci, bacteroides, and clostridia. Total counts of all organisms were reported as less than detectable [less than 100 Colony Forming Units (CFU)/gram stool] or detectable (> 100 CFU/gram stool). Presence of *Clostridium difficile* toxin was detected with a standard enzyme immunoassay. Tolerance of formula was assessed by interview and a diary record (24 hours once a week).

Study results: A total of 87 infants were enrolled in the study, and 72 completed it and were considered eligible for the per-protocol evaluation. Of those who completed the study, 14 infants were fed human milk throughout the study, and 58 infants were each randomly assigned to one of four formula-fed groups (28 infants with the 1.5 g/L FOS formula and 30 infants with the 3.0 g/L FOS formula). The five study groups did not differ with respect to mean gestational age, weight, length and head circumference at birth and mean baseline age (4.5 weeks).

Prior to the start of FOS supplementation in formulae, the human milk-fed and formula-fed groups had similar *Bifidobacterium* and *Lactobacillus* counts in their stools and these did not change after the addition of FOS to formula. All formula-fed groups had approximately 100-fold higher *Enterococcus* and *Bacteroides* counts compared with the human milk-fed group at the visit prior to FOS supplementation. The difference was highly significant (*Enterococcus* p=0.0001; *Bacteroides* p=0.018). After FOS supplementation these counts changed independent of the dose but remained significantly different compared with the human milk-fed group seven days later (100-fold higher). *Clostridium* counts were similar for the human milk-fed group and the formula-fed groups before FOS supplementation and immediately after FOS supplementation. Seven days after the conclusion of the FOS supplementation *Clostridium* counts were highest in the 1.5 g/L FOS formula group and similar for the human milk-fed group and 3.0 g/L FOS formula group.

No human milk-fed infants had detectable *Clostridium difficile* toxin at any time during the study. From the visit before FOS supplementation of infant formula to the visit after FOS supplementation of infant formula, groups fed 1.5 g/L and 3.0 g/L FOS experienced a similar decline in the proportion of infants with *Clostridium difficile* toxin. Differences among the human milk-fed and the formula-fed groups before, immediately and seven days after FOS supplementation were not significant.

Of the infants enrolled, more formula-fed infants [1.5 g/L FOS: n= 30 (83%); 3g/L FOS: n=33 (97%)] experienced adverse events than human milk-fed infants; n=10 (59%)]. The most commonly experienced adverse events during the study were those involving the gastrointestinal tract. To demonstrate a potential relationship to FOS-supplemented study formula, adverse events were tabulated for the week prior and the week during FOS supplementation. During the week of FOS supplementation, formula-fed infants experienced increased flatulence, increased spit-ups, and looser stools, compared with human milk-fed infants (Table 1). The incidence of these adverse events was lower in the 1.5 g/L FOS group than in the 3.0 g/L FOS group during the week of FOS supplementation.

Table 1. Adverse events occurring during the week of FOS supplementation by treatment group (intention-to-treat population)

	Human milk (n=15)	FOS 1.5 g/L (n=33)	FOS 3 g/L (n=32)	p value*
Increased flatulence	0 (0%)	7 (21%)	10 (31%)	0.034
Increased spit-ups	0 (0%)	4 (12%)	9 (28%)	0.036
Irritability	1 (7%)	4 (12%)	6 (19%)	0.59
Looser stools	0 (0%)	5 (15%)	10 (31%)	0.024

* Anova (between groups)

Two infants (6%) in the 3.0 g/L FOS group experienced serious adverse events, both of which were considered in the dossier as possibly formula-related. Three infants (8.3%) in the 1.5 g/L FOS group and one infant (2.9%) in the 3.0 g/L FOS group also experienced adverse events that led to permanent discontinuation of study formula.

Prior to FOS supplementation of formula, the human milk-fed group had on average more frequent bowel movements per day than the formula-fed groups (Human milk: n=5.1; 1.5 g/L FOS: n= 2.0; 3.0 g/L FOS: n=1.6). Stools were looser for the human milk-fed group. After FOS supplementation, the frequency of bowel movements in infant formulae-fed infants was on average still significantly lower and the stools were firmer compared with human milk-fed infants. However, in some infants high numbers of stools per day were seen with FOS. The maximum number of daily stools observed in the FOS 3.0 g/L supplemented group was 11.

Satisfaction ratings for study formula acceptability and tolerance declined at the visit after FOS supplementation and were slightly higher for the 1.5 g/L FOS group than the 3.0 g/L group. No such satisfaction ratings were given for the human milk-fed group.

Summary and comment: The primary objective of the study could not be fulfilled. Prior to the supplementation with FOS, there was no difference in the stool counts of bifidobacteria and lactobacilli between human milk-fed infants and infants fed infant formula. An increase of bifidobacteria in the stools of the FOS supplemented infants was not observed with 1.5 g/L or 3.0 g/L of FOS in infant formula, nor was the pattern of faecal microbiota closer to that of human milk-fed infants. The secondary objective could not be fulfilled. Supplementation with either 1.5 g/L or 3.0 g/L of FOS did not have any influence on the stool counts of enterococci, bacteroides, and clostridia, and of *Clostridium difficile* toxin-positive stools. Moreover, the use of FOS did not result in an occurrence of *Clostridium difficile* toxin-positive stools similar to that in human milk-fed infants. The tertiary objective was not fulfilled, since the use of FOS was not associated with continuing bifidogenic microbiota changes and a lower occurrence of *Clostridium difficile* toxin-positive stools.

In one other randomised controlled study in which up to 3 g/day of unspecified FOS was added to an infant formula, no bifidogenic effect was demonstrated (Guesry *et al.*, 2000).

These results are different to the reported bifidogenic effect of FOS in adults (Van Loo *et al.*, 1999).

In contrast, a mixture of 10% FOS - 90% GOS which was studied at concentrations of 4, 8, or

10 g/L in infant formula in preterm and term infants (Boehm *et al.*, 2002; Moro *et al.*, 2002; Schmelzle *et al.*, 2003), resulted in significant increases of total faecal bifidobacteria and/or significant increases of the proportion of faecal bifidobacteria as a percentage of total faecal microorganisms. This effect was dose-dependent and greater with a concentration of FOS/GOS of 8 g/L of formula than of 4 g/L (Moro *et al.*, 2002). It is, however, not possible to conclude from these data to what extent the GOS or the FOS are responsible for the observed effects.

The use of FOS and GOS may also increase stool frequency and reduce stool consistency in infants. In one open study, term infants with a mean age of 7 weeks fed a formula with 8 g/L of a 10% FOS - 90% GOS mixture, showed watery or fluid stools in 27%, compared to 12% in a control group fed regular infant formula (Veitl *et al.*, 2000).

Low stool consistency in breast-fed infants is not of concern since human milk has a lower renal solute load than infant formula. However, the possible induction of liquid and fluid stools by FOS and GOS in formula-fed infants may increase faecal water losses which might put some infants at risk of dehydration (SCF, 2001a). The SCF concluded that there was no indication of adverse effects from the use of a formula with up to 8 g/L of a combination of 90% GOS and 10% FOS (i.e. 0.8 g/L of FOS) (SCF, 2001b). However, this conclusion does not apply to the single use of FOS in infant formula at a concentration of 1.5 or 3.0 g/L, which is 1.875 and 3.75-fold higher, respectively, than the level of FOS evaluated by the SCF (SCF, 2001b).

Safety concerns are raised because of the higher prevalence of flatulence, increased spit-ups and looser stools in some FOS supplemented infants. As no measures were made to demonstrate satisfactory water balance, a risk of dehydration in neonates cannot be ruled out in specific conditions.

CONCLUSIONS AND RECOMMENDATIONS

The data submitted indicate:

1. In the growth study, the anthropometric data suggest that the use of infant formula supplemented with either 1.5 or 3.0 g/L of fructooligosaccharides results in a normal growth pattern in healthy term infants less than two weeks of age for periods of up to twelve weeks. Serum markers of protein and mineral status and kidney function were also in the normal range.

2. No effect of fructooligosaccharides in rendering the faecal microbiota more similar to that in human milk-fed infants was demonstrated in infants fed an infant formula supplemented with either 1.5 or 3.0 g/L of fructooligosaccharides for one week.

3. 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.

As no data have been submitted nor were available from the literature on the use of fructooligosaccharides in follow-on formula, the Panel is not in the position to evaluate the safety and suitability of FOS for such use.

DOCUMENTATION PROVIDED TO EFSA

Dossier submitted by Wyeth Nutrition to the European Commission for an amendment to Commission Directive 91/321/EEC to include fructooligosaccharides as an ingredient in infant formulae and follow-on formulae, April 2003.

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ACKNOWLEDGEMENT

The Scientific Panel on Dietetic Products, Nutrition and Allergies wishes to thank Dominique Turck for his contribution to the draft opinion.