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Statement on the use of resistant short chain carbohydrates (oligofructose and oligogalactose) in infant formulae and in follow-on formulae

(expressed on 26 September 2001)

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Statement on the use of resistant short chain carbohydrates (oligofructose and oligogalactose) in infant formulae and in follow-on formulae

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Terms of reference

The Commission has asked the SCF to comment urgently on the suitability and safety of the resistant short chain carbohydrates, oligofructosyl-saccharose (oligofructose; fructooligosaccharides; FOS) and oligogalactosyl-lactose (oligogalactose; galactooligosaccharides; GOS), in infant formulae and follow-on formulae, within the wider context of a review on the essential composition of infant formulae as given in the Directive 91/321/EEC.

Background

On the request of Member States, a discussion took place in the Standing Committee of Foodstuffs regarding the marketing, in most Member States, of dietary products for infants sold either as infant formulae and follow-on formulae, or as foods for special medical purposes, containing the short chain carbohydrates, oligofructosyl-saccharose (oligofructose; fructooligosaccharides; FOS) and oligogalactosyl-lactose (oligogalactose; galactooligosaccharides; GOS).

France informed the other Member States and the Commission in the Standing Committee on Foodstuffs that they had asked AFSSA (*Agence Française de Sécurité Sanitaire des Aliments*, the French Food Safety Agency) to give its assessment on such products marketed in France. On 9 January 2001 and on 10 July 2001 AFSSA delivered opinions on the issue.

The Scientific Committee on Food reviewed this question taking into account generally accepted scientific knowledge and data provided by manufacturers, within the framework of an ongoing revaluation of the essential requirements of infant formulae and follow-on formulae. The Committee requested from the industry comprehensive information regarding technical data on resistant short chain carbohydrates (e.g. identity of source(s), specifications, manufacturing process, analytical methods in foods, reaction and fate in food, case of need and proposed uses, exposure data, existing national authorisations), biological data (physiological and nutritional effects, potential adverse effects) and all the relevant data from experimental, pre-clinical and clinical studies particularly in infants.

Evaluation

<u>Characterisation of the short chain carbohydrates (SCC) under discussion</u>

Oligofructose is produced from chicory roots and contains one molecule of saccharose with between 1 and >60 added fructose molecules. Oligogalactose is produced from lactose with the help of a bacterial ß-galactosidase, it contains one molecule of glucose and typically between 1 and 7

molecules of galactose. In addition to oligogalactose, the preparation used in dietetic products for infants contains some 40 % (wt/wt) of mono- and disaccharides. Oligofructose has a sweet taste considered to be about 0.3 times as sweet as sugar (Wiedmann and Jager, 1997). The preparations of resistant SCC under discussion here are partly digestable and have an utilisable caloric value (Carabin and Flamm, 1999).

Human milk contains a complex mixture of more than 100 different oligosaccharides in small amounts, which among other functions may also serve as substrates for colonic fermentation (Kunz *et al.*, 1999). Oligofructose is not found in human milk. Oligogalactose is found only in trace amounts in human milk.

Effects on stool flora

Dietary short chain carbohydrates (SCC) that are resistant to digestion in the human intestinal tract, such as oligofructose, may promote the growth of bifidobacteria and lactobacilli in the colon and thus induce prebiotic effects in adults (Cummings *et al.*, 2001; Salminen *et al.*, 1998; Bouhnik *et al.*, 1999). Breast fed infants typically show a Bifidus-dominated flora. In infants, the promotion of a Bifidus-dominated flora is considered to have beneficial effects, such as some protection against enteric infections.

The Committee reviewed the results of presented studies using low-molecular weight oligofructose or a mixture of oligogalactose and high-molecular weight oligofructose, with a total number of less than 300 infants studied. Studies in human infants with low-molecular weight oligofructose, using formulae with matched contents of lactose as controls, failed to find significant effects on bifidobacteriae counts in stools. In contrast, in two short-term studies the addition of 0.4 g/dL or 0.8 g/dL of a mixture of SCC (90 % oligogalactose, 10 % high-molecular weight oligofructose) increased stool counts of bifidobacteriae and lactobacilli in preterm and term infants, relative to diets with matched contents of maltodextrin, and partly also other differences in dietary composition. The effects on the stool flora were similar at the two dosages used, 0.4 g/dL or 0.8 g/dL. However, at this time there is little conclusive evidence on the relationship between a bifidobacteria-dominated flora and relevant outcomes on health and well being in infants, which will be considered in more detail in the ongoing evaluation of the essential requirements of infant formulae and follow-on formulae.

Stool frequency, consistency, and water balance

In a dose dependent manner, resistant SCC increased stool frequency and reduced stool consistency in infants, with the induction of more watery stools. Both stool frequency and stool consistency differed significantly with the use of two concentrations of 0.4 g/dL or 0.8 g/dL, respectively, of the mixture of 90 % oligogalactose and 10 % oligofructose. In one open study in term infants, infants with a mean age of 7 weeks fed a formulae diet with 0.8 g/dL SCC, as well as modified protein, fat and lactose contents, showed watery or fluid stools in 27 %, compared to 12 % in a control group fed regular infant formulae (Veitl *et al.*, 2000). Although stools with low consistency are common in breast fed infants, human milk has a far lower renal solute load than infant formulae. The possible induction of liquid and fluid stools by dietary SCC in formulae fed infants may increase faecal water losses.

The Committee is concerned that the addition of SCC in a dosage that increases stool frequency and reduces stool consistency might put some infants at risk of dehydration. A particular risk may exist for infants during the first months of life with renal immaturity and a poor ability to concentrate urine, especially if an additional stress on water balance is induced, for example by fever, hyperventilation resulting from pulmonary disorders, infectious diarrhoea, high dietary renal solute

loads, or refusal of the infant to accept appropriate quantities of fluids. Young infants have a very high water turnover, in the order of 200 ml/kg and day during the first two months of life (Goellner *et al.,* 1981). Interference with water balance may put young infants at risk of hypernatriaemic dehydration, as is exemplified by the relationship between dietary renal solute load and incidence rates of hypernatriaemic dehydration observed in the United Kingdom in the seventies (Arneil and Chin, 1979; Sunderland and Emery, 1979; Manuel and Walker-Smith, 1980; Davies *et al.,* 1979). No data are available on direct or indirect measures of water balance neither in healthy infants, nor in infants under additional stress factors that may affect water balance, who are exposed to different dosages of dietary resistant SCC.

While an adequate safety evaluation with respect to effects on water balance is also not available for older infants after the first 4-6 months of life, the Committee considers the adverse potential of the aforementioned effects to be very low in this age group. In the older age group, infants have a lower water turnover per unit body weight, show a more mature renal function, and are usually fed a mixed diet with other sources of fluid, in addition to formulae.

Other safety aspects

An induction of a more rapid intestinal transit and of loose stools by dietary SCC in infants might interfere with the bioavailability of substrates. In an ongoing controlled trial in term infants, an interim analysis revealed lower serum concentrations of prealbumin in infants fed a formulae diet with 0.8 g/dL SCC than in the control group, which may or may not be related to a modulation of nitrogen retention. No systematic evaluation of the effects of dietary SCC on the absorption of macro- and micronutrients in infants has been performed. Some data on effects of dietary products with added SCC on growth are available, but the data are limited and include only short-term observations.

Young infants have an immature gut barrier and are considered at increased risk for allergic sensitisation. In view of a report on anaphylactic reactions to inulin and oligofructose in a single adult case (Gay-Crosier *et al.,* 2000), the potential of sensitisation should be monitored in future evaluations.

Observations in animals

Some studies in non-pregnant and in pregnant rats fed diets with added oligofructose showed a dose-dependant induction of loose and watery stools, and a reduced body weight (Carabin and Flamm, 1999). The effects on body weight might be related either to an interference with substrate absorption, or water homeostasis, or a combination of both. In a further feeding study, 50 male and 50 female rats received diets providing 0, 0.34-0.42, 0.85-1.0, or 2.2-2.7 g/kg per day oligofructose. Male rats exposed to oligofructose showed significant elevations of serum concentrations of sodium and chloride, and in some cases showed pathological changes of the kidneys, including degeneration of proximal tubular epithelial cells. Only the male rats receiving 0.85 g/kg also showed a significant increase of serum creatinine as well as increased mortality (Carabin and Flamm, 1999). In two studies in rats exposed to dietary oligofructose, caecal enlargements were noted (Carabin and Flamm, 1999). Although conclusions cannot be directly extrapolated from these observations to infants, they illustrate possible adverse effects of dietary SCC on water balance.

Conclusions

The issue of whether the inclusion of suitable resistant SCC may induce beneficial effects in the recipient infants will be reviewed further, within the ongoing evaluation of the essential requirements of infant formulae and follow-on formulae.

The Committee concludes that there are insufficient data to establish the safe use of oligofructosyl-saccharose (oligofructose; fructooligosaccharides; FOS) and oligogalactosyl-lactose (oligogalactose, galactooligosaccharides; GOS) as ingredients of infant formulae, which serve as the sole diet of infants during the first months of life. Appropriate studies should evaluate the potential of adverse effects, particularly with respect to water balance and nutrient bioavailability.

The Committee considers the potential for adverse effects in older infants to be very low. Therefore, the Committee finds it acceptable, for the time being, to use oligofructosyl-saccharose (oligofructose; fructooligosaccharides; FOS) and oligogalactosyl-lactose (oligogalactose, galactooligosaccharides; GOS) as ingredients of follow-on formulae intended for use in older infants, in a concentration of up to 0.8 g/dL of product ready for consumption.

The Committee recommends that additional information on the suitability and safety of resistant SCC be submitted, with particular attention to possible effects on water balance. The Committee intends to review the use of SCC in infant formulae and follow-on formulae as soon as significant new data become available.

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