

**ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES****D-TAGATOSE****Issue**

At the last meeting Members discussed the draft opinion for D-tagatose. Members highlighted a number of comments and also sought clarification from the applicant that the gastrointestinal effects observed in adults would be seen in children at similar dose levels. Members are asked whether the applicant's response offers reassurance that the effects seen in children would be similar to those seen in adults, and whether they are content that the changes to the draft opinion reflect the discussion at the last meeting.

**Background**

1. An application has been submitted by Bioresco, acting on behalf of Arla Food Ingredients, Denmark for authorisation of D-tagatose as a novel ingredient in the EU. The application was accepted by the UK Competent Authority on the 1<sup>st</sup> March 2005. In accordance with Article 6(3) of Regulation (EC) No 258/97, the UK has 3 months to prepare an initial assessment report on the above application. The initial assessment will then be circulated for review by the Competent Authorities in the other Member States (MS).
2. D-Tagatose is a monosaccharide, an enantiomer of D-fructose (inversion at C-4), which is not commonly found in food, although it is found at low levels in heat-treated dairy products such as sterilised and dried milk. D-tagatose has 75-92% the sweetness of sucrose and behaves like other sugars in terms of hygroscopicity, and stability under low pH and raised temperature (Appendix 1 p15). Its principal purpose is as a carbohydrate source that is non-cariogenic, and as a prebiotic.
3. Members have previously indicated that they are content that there are no specific concerns regarding this application. Concerning labelling, Members agreed with the applicant that the consumption of more than 15g of D-tagatose in a single serving is appropriate to require labelling to highlight potential laxative effects. However, this figure was determined on the basis of a number of studies using healthy adults and Members therefore requested reassurance that this figure should apply equally to children.
4. The applicant has now provided additional information that they believe offers sufficient reassurance that the 15g figure is also appropriate for children. The applicant also highlights that, based on their anticipated uses of tagatose, the predicted 90<sup>th</sup> percentile in all age groups is considerably lower than the 15g per serving.

5. There are no scientific studies that look at possible gastrointestinal effects of excessive consumption of tagatose in children, and there are ethical reasons that would, in all likelihood, prevent the applicant from carrying out such studies. In view of this the applicant has carried out a literature review of studies carried out on two polyols (xylitol and sorbitol) that have similar levels of fractional absorption. The Applicant has responded to the question of intestinal intolerance in children and adults separately (Appendix 1a and 1b respectively). Members should also note that in Appendix 1b, a table summarising a number of xylitol tolerance studies in adults, also includes additional studies involving children. The covering letter also refers to a number of other adult studies and these, together with the scientific papers are also included in Appendix 1b.
6. The applicant also notes that a review of a 1999 symposium investigating the effects of low digestible carbohydrates concluded that there is no reason to set different intestinal thresholds for children and adults.
7. The Secretariat is of the view that although the data do indicate varied responses, these are not necessarily linked to age, and support the applicant's intention to include advisory labelling on any future products that contain >15g per serving. The Secretariat has therefore redrafted the initial opinion to take account of this, and other drafting comments raised by members at the last meeting.

### **Committee Action required**

8. The Committee is invited to consider and comment on the draft initial opinion of the application attached at Appendix 2 and to indicate whether the information supplied by the applicant is sufficient to complete its assessment of this product. If not the Committee is asked what additional information is required.
9. Once the text is agreed, the draft initial opinion will be published via the website for a short period of public comment. The Committee's final initial assessment will be forwarded to the Commission as the basis for the UK's formal assessment report on this application.
10. The Secretariat requests comments not later than **Friday the 15<sup>th</sup> July**.

**Secretariat  
July 2005**

### **Appendices attached:**

- Appendix 1:** Additional information supplied by the applicant.
- (a) Letter to Secretariat re: GI effects in children.
  - (b) Letter to Secretariat re: GI effects in adults.

**Appendix 2:** Draft initial Opinion (restricted)

**ADVISORY COMMITTEE ON NOVEL FOODS AND PROCESSES**

Additional information supplied by the applicant.

- (a) Letter to Secretariat re: GI effects in children
- (b) Letter to Secretariat re: GI effects in adults

**Secretariat  
July 2005**

*Bioresco*  
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Basel, June 1, 2005

D-Tagatose

Dear Chris

I understand from your earlier telephone call and your subsequent e-mail that the ACNFP wished to get assurance that D-tagatose under the intended conditions of use would not induce symptoms of intestinal intolerance in children and that also children would be adequately protected by a warning label about possible intestinal effects on foods containing more than 15 g D-tagatose per serving.

The calculation of the estimated intake of D-tagatose from its intended uses indicates that the intake per eating occasion is highest at breakfast (see Table 3 of our Dossier). The 90<sup>th</sup> percentile ("heavy") consumer of the 2 - 5 year and 6 - 12 year age group ingests 5.8 and 6.0 g D-tagatose at breakfast. These intakes are far below the 15-g level (single dose), above which a warning statement about potential laxative effects may be warranted.

The intake of single doses of 15 g D-tagatose was found to be well tolerated by adult volunteers (see section 9.3.1 of our Dossier). While studies of the intestinal tolerance of D-tagatose in children have not been conducted, there is indirect evidence that the 15 g single dose will not result in untoward intestinal effects also in children. This indirect evidence is derived from the following considerations and data.

The intestinal tolerance of low digestible polyols and sugars is limited because their not absorbed fraction attracts water into the intestinal lumen by means of an osmotic effect. The laxative potential of a low digestible polyol or sugar is, therefore, inversely related to its rate of absorption in the small

intestine. In the large intestine, any not absorbed polyol or sugar is eliminated by microbial fermentation, i.e. the osmotic activity of these products disappears. Accordingly, borborygmi, nausea and laxative effects in response to the ingestion of excessive amounts of polyols occur typically within the first one to two hours after ingestion, i.e. during small intestinal passage. In contrast, flatulence occurs later when not absorbed polyols or sugars reach the lower, microbially colonized parts of the GI tract.

The intestinal tolerance of D-tagatose has been examined in adults but not in children. However, data on the laxative effects of polyols with a similar degree of malabsorption can be used for estimating the intestinal tolerance of D-tagatose in children.

Xylitol and sorbitol are particularly well suited substances for comparison because their fractional absorption is similar to that of D-tagatose and their intestinal tolerance has been examined in children.

The fractional absorption of D-tagatose in humans has been estimated at 20% (see Section 9.1.1.3 of our Dossier). The absorption of sorbitol may be slightly lower because this hexitol is slightly more hydrophilic than D-tagatose. It has been estimated at 17.5% (Bär, 1990 as cited in the Dossier). The absorption of xylitol may be slightly higher than that of D-tagatose because the molecular volume of this pentitol is somewhat smaller. It has been estimated at 33% (Bär, 1990 as cited in the Dossier).

In a summer camp, the tolerance of sorbitol was investigated in 205 type-1 diabetic boys of whom 143 ingested 41 g sorbitol daily divided in 3 single doses with their main meals for a period of 8 - 48 days. In comparison with the 62 controls, diarrhea did not occur more frequently in the sorbitol group (Steinke et al., 1961).

The tolerance of increasing doses of xylitol was examined in 13 healthy children aged 7 - 16 years. At an intake of 10 g/d (1 chocolate bar plus 4 chewing gums) side effects (flatulence) were reported not more often than in the two control periods without xylitol intake. At a daily xylitol intake of 25 g/d (4 wafers, 1 chocolate bar, 4 gums), abdominal pain was reported on 7 occasions (4 children) (control periods: 2 occasions, 2 children). At an intake of 45 g/d, flatulence was reported significantly more often, but abdominal pain was recorded with similar frequency as during the control periods (2 occasions). Laxative

effects occurred only when the xylitol intake rose to 65 g (4 occasions in 4 children) (Akerblom et al, 1981).

It follows from these studies that not only adults but also children will tolerate an intake of 15 g (45 g/day) D-tagatose per eating occasion without untoward intestinal effects.

I hope this information will help you address the remaining question of your expert panel.

With best regards

Bioresco Ltd.



Dr. Albert Bär

References:

Akerblom H.K., Koivukangas T., Puukaa R. and Mononen M. (1981). The tolerance of increasing amounts of dietary xylitol in children. *Int. J. Vitam. Nutr. Res. Suppl.* 22: 53 - 66.

Steinke J. and Wood F.C. (1961). Evaluation of sorbitol in the diet of diabetic children at camp. *Diabetes* 10: 218 - 227.

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Basel, June 8, 2005

Tolerance of xylitol and sorbitol in adults

Dear Chris

There are a number of studies on the intestinal tolerance of sorbitol and xylitol. However, most of them were conducted before 1990. The difficulty in reviewing these studies is that quite different experimental conditions were applied by the different investigators and that often only the tested total daily dose, but not the much more relevant single dose, was reported.

I have reviewed the pertinent literature for another purpose in 1993. A list of the then reviewed studies on xylitol is attached. My conclusion from these data is that a single dose of 20 g xylitol is usually well tolerated by adults without significant gastrointestinal side effects. At 25 g single dose, unpleasant symptoms may occur in some people who are particularly sensitive to such effects (Born et al., 1994).

The tolerance in adults of sorbitol is not much different from that of xylitol. Single doses of 20 g produce no, or only very mild gastrointestinal side effects (Beaugerie et al., 1991, 1994; Vernia et al., 1995).

At higher doses (31.5 g single dose), mild diarrhea may be experienced by some individuals (Lee et al., 1994).

A review on the tolerance of low-digestible carbohydrates has been prepared by Geoffrey Livesey for a Symposium on low-digestible carbohydrates held at the University of Salford in 1999 (Storey & Lee, 2001; Livesey, 2001). His conclusion was that there is no reason for setting the threshold of intestinal tolerance at different levels for adults and children (8 years of age). In his estimation, single doses of 10, 20 and 30 g for

mono- di- and oligosaccharides, would be well tolerated by the vast majority of consumers.

According to our Dossier on D-tagatose, the projected intake per eating occasion of this sugar is 3.1 and 6.2 g/person for the mean and 90<sup>th</sup> percentile consumer. This dose is well below the proposed threshold doses for intestinal effects of other low-digestible carbohydrates with similar molecular size and thus similar fractional absorption, such as sorbitol and xylitol.

Hoping that these additional data will help your expert panel to conclude its safety assessment of D-tagatose, I remain

With best regards

Bioresco Ltd.



Dr. Albert Bär

References:

Beaugerie L., Flourié B., Pellier P., Achour L., Franchisseur C. and Rambaud J.-C. (1991). Tolérance clinique, absorption intestinale et valeur énergétique de quatre polyols pris à jeun. Gastroenterol. Clin. Biol. 15: 929 - 932.

Beaugerie L., Flourié B., Lémann M., Achour L., Franchisseur C. and Rambaud J.-C. (1994). Sorbitol absorption in the healthy human small intestine is increased by the concomitant ingestion of glucose or lipids. Eur. J. Gastroent. Hepatol. 7: 125 - 128.

Born P., Zech J., Stark M., Classen M. and Lorenz R. (1994). Zuckeraustauschstoffe: Vergleichende Untersuchung zur intestinalen Resorption von Fructose, Sorbit und Xylit. Med. Klin. 89: 575 - 578.

Lee A., Zumbo A. and Storey D. (1994). Breath hydrogen after ingestion of the bulk sweeteners sorbitol, isomalt and sucrose in chocolate. *Brit. J. Nutr.* 71: 731 - 737.

Livesey G. (2001). Tolerance of low-digestible carbohydrates: a general view. *Brit. J. Nutr.* 85(1): S7 - S16.

Vernia P., Frandina C., Bilotta T., Ricciardi M.R., Villotti G. and Fallucca F. (1995). Sorbitol malabsorption and nonspecific abdominal symptoms in type II diabetes. *Metabolism* 44(6): 796 - 799.