Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

D-Tagatose

Tweede beoordeling van de veiligheid voor de consument, volgens de Europese verordening 258/97 betreffende nieuwe voedingsmiddelen en nieuwe voedselingrediënten

Second opinion regarding consumer safety, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

aan/to:

de Minister van Volksgezondheid, Welzijn en Sport
the Minister of Health, Welfare and Sport

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Bureau Nieuwe Voedingsmiddelen
CBG
Postbus 16229
2500 BE Den Haag
novelfoods@cbg-meb.nl
www.nieuwevoedingsmiddelen.nl

Novel Foods Unit
MEB
P.O. box 16229
2500 BE The Hague
The Netherlands
novelfoods@cbg-meb.nl
www.novel-foods.nl

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Beoordeling

Inleiding

Aan de orde is een tweede beoordeling volgens de Europese Verordening 258/97, over het gebruik van D-tagatose als een nieuw voedselingrediënt. De aanvraag is ingediend door de firma Bioresco namens Arla Food Ingredients (Denemarken), de firma die dit nieuwe voedselingrediënt op de Europese markt wil brengen. D-tagatose is een monosaccharide en enantiomeer van D-fructose. De stof komt van nature niet in voedingsmiddelen voor, maar is wel in lage gehaltes aanwezig in verhitte melkproducten. Op Europees niveau is er discussie geweest over de vraag of D-tagatose als zoetstof moest worden gezien, waarvoor een autorisatie als voedseladditief vereist is. Het Europese Permanent Comité voor de Voedselketen en de Diergezondheid concludeerde echter dat D-tagatose als nieuw voedingsmiddel moet worden beschouwd[1]. In het kader van de desbetreffende toelatingsprocedure is deze tweede beoordeling uitgevoerd door het Bureau Nieuwe Voedingsmiddelen van het College ter Beoordeling van Geneesmiddelen. Het bureau heeft hiervoor de Commissie Veiligheidsbeoordeling Nieuwe Voedingsmiddelen geraadpleegd, hierna genoemd ‘de commissie VNV’.

Eerste beoordeling

De eerste beoordeling van de aanvraag voor markttoelating is verricht in het Verenigd Koninkrijk door de *Advisory Committee on Novel Foods and Processes* (ACNFP) van de *Food Standards Agency*. De ACNFP concludeert dat de door de aanvrager verstrekte informatie voldoende aantoont dat het product D-tagatose veilig is voor de consument. De ACNFP heeft dan ook geen bezwaar tegen markttoelating, mits voldaan wordt aan de voorgestelde specificatie. Wel wijst de ACNFP erop dat voedingsmiddelen met D-tagatose ook moeten voldoen aan de Europese etiketteringsverplichting voor bepaalde voedselallergenen. Ook spreekt de ACNFP zich uit over etikettering van voedingsmiddelen met D-tagatose in verband met een mogelijk laxerend effect van inname van grotere hoeveelheden D-tagatose in één keer en in verband met de vereiste vermelding van de energiewaarde voor suikers.

Bevindingen van de commissie VNV

De commissie VNV heeft geen bezwaar tegen de toelating van D-tagatose als nieuw voedselingrediënt. Zij baseert haar oordeel op de informatie in het dossier (zie de samenvatting in bijlage A) en de eerste beoordeling van de ACNFP (bijlage B). Tevens

[1] Standing Committee on the Food Chain and Animal Health, Section on Toxicological Safety. Summary report of the meeting of 17 December 2004. (http://www.europa.eu.int/comm/food/committees/regulatory/scfcah/toxic/agenda16_en.pdf)

heeft zij gebruik gemaakt van informatie van de *Joint FAO/WHO Expert Committee on Food Additives* (JECFA)[2].

De commissie VNV is het eens met de ACNFP het productieproces geen aanleiding geeft tot bedenkingen en het eindproduct voldoende is gespecificeerd. Het uitgangsmateriaal voor de productie is lactose, dat door het geïmmobiliseerde enzym lactase wordt gesplitst in galactose en glucose. Vervolgens wordt met behulp van een ionenwisselaar een fractie geïsoleerd, waarin zich de galactose bevindt. Galactose wordt omgezet in D-tagatose door toevoeging van calciumhydroxide. Daarna vindt verdere opzuivering plaats tot een eindproduct met meer dan 98% D-tagatose. Hierin is bij HPLC analyse alleen enige galactose als bijproduct detecteerbaar.

De aanvrager richt zich op een wereldwijde toepassing van D-tagatose in een breed assortiment voedingsmiddelen, dat niet beperkt wordt tot bijzondere groepen consumenten. De aanvrager geeft een lijst van voorgestelde gehaltes D-tagatose in verschillende voedingsmiddelen. Deze gegevens gebruikt de aanvrager in combinatie met voedselconsumptiegegevens uit de Verenigde Staten, om een inschatting te maken van de verwachte inname van D-tagatose. De ACNFP berekende uit deze gegevens en voedselconsumptiegegevens uit het Verenigd Koninkrijk de geschatte inname voor verschillende leeftijdsgroepen (weergegeven op pagina 7 van de eerste beoordeling). De schattingen voor de gemiddelde inname varieerden van 2,8 tot 5,6 gram per persoon per dag. De hoogste schatting van de inname bedraagt 11,9 gram per persoon per dag (voor het 97,5 percentiel bij kinderen van 6-12 jaar in het Verenigd Koninkrijk). De ACNFP plaatst hierbij de kanttekening dat de inname hoger kan worden door een bredere toepassing of door verhoging van het gehalte D-tagatose in voedingsmiddelen. Ook de commissie VNV is van mening dat bij een toelating rekening moet worden gehouden met een mogelijk nog ruimere toepassing.

Door onvolledige absorptie in het maagdarmkanaal heeft D-tagatose een lagere energiewaarde dan sucrose. De commissie deelt de mening van de ACNFP dat dit niet van invloed is op de veiligheidsbeoordeling. De ACNFP wijst er nog op dat op het etiket wettelijk een hogere energiewaarde voor suikers moet worden vermeld.

De commissie VNV onderschrijft de conclusie van de ACNFP dat uit het dossier geen bezwaren ten aanzien van microbiële veiligheid naar voren komen.

Een uitgebreide toxicologische beoordeling van D-tagatose is uitgevoerd door de JECFA. De bevindingen van de JECFA zijn ook van toepassing op de beoordeling van dit dossier. Nadat de JECFA bij eerdere beoordelingen een voorlopige *Acceptable Daily Intake* (ADI) had vastgesteld, heeft zij na bestudering van additionele gegevens in 2004 de status "*ADI not specified*" toegekend voor D-tagatose. Dit betekent dat de JECFA op basis van de beschikbare informatie over de eigenschappen en het voorgestelde gebruik van deze stof geen gezondheidsrisico voorziet[3]. Daarbij is in aanmerking genomen dat D-tagatose vergelijkbare fysiologische en toxicologische eigenschappen heeft als andere

[2] Evaluation of certain food additives. WHO Technical Report Series #928, p. 39-42. (http://whqlibdoc.who.int/trs/WHO_TRS_928.pdf)

[3] Principles for the safety assessment of food additives and contaminants in food. (http://www.inchem.org/documents/ehc/ehc/ehc70.htm)

minder goed verteerbare koolhydraten. De commissie VNV onderschrijft evenals de ACNFP deze conclusie van de JECFA. De JECFA vermeldt tevens dat de status "*ADI not specified*" niet van toepassing is op individuen die lijden aan bekende, maar zeldzame erfelijke afwijkingen in het fructosemetabolisme, te weten fructose intolerantie (fructose–aldolase deficiëntie, incidentie 1:20.000) en fructose 1,6-diphosphatase deficiëntie (incidentie onbekend) [4]. Mensen met een dergelijke aangeboren stofwisselingstoornis kunnen géén of maar weinig fructose verdragen. De aanvrager stelt in het dossier dat deze personen ook zullen reageren op D-tagatose, maar dat het effect kleiner zal zijn door de verlaagde absorptie. De aanvrager meent dat het niet nodig is om een bijzondere waarschuwing te vermelden op het etiket van voedingsmiddelen met D-tagatose. De ACNFP spreekt zich in haar advies hierover niet uit. De commissie VNV is van mening dat het voor deze groep consumenten belangrijk is om producten met D-tagatose te kunnen herkennen.

Verder blijkt uit de gegevens van de aanvrager dat de onvolledige absorptie bij hiervoor gevoelige personen kan leiden tot een laxerend effect, bij gebruik van meer dan 15 gram D-tagatose in één keer. De aanvrager stelt voor om een waarschuwing op te nemen op de verpakking van producten met meer dan 15 gram D-tagatose per portie. De ACNFP ondersteunt dit voorstel voor vaste voedingsmiddelen, maar beveelt tevens aan om voor frisdranken een vermelding op te nemen bij gehaltes van meer dan 1% D-tagatose.

Conclusie

Samenvattend is de commissie VNV het eens met de conclusie van de eerste beoordeling door de ACNFP, dat D-tagatose veilig kan worden gebruikt voor de toepassingen die in het dossier zijn beschreven. De commissie heeft kennis genomen van de genoemde aandachtspunten ten aanzien van mogelijke etikettering van voedingsmiddelen met D-tagatose, maar wijst erop dat etikettering in Nederland wordt besproken in het Regulier Overleg Warenwet. Wel vindt zij het belangrijk dat producten met toegevoegd D-tagatose herkenbaar zijn als ongeschikt voor mensen met bepaalde zeldzame erfelijke afwijkingen van het fructosemetabolisme.

[4] Te onderscheiden van essentiële fructosuria (fructokinase deficiëntie, incidentie 1:130.000), een onschuldige erfelijke stofwisselingstoornis die niet als een ziekte wordt beschouwd.

English courtesy translation

Introduction

The subject in question is a so-called second opinion, in accordance with European Regulation 258/97, regarding the use of D-tagatose as a novel food ingredient. The applicant is the company Bioresco, acting on behalf of Arla Food Ingredients (Danmark), which is the company intending to market this novel food ingredient in Europe. D-tagatose is a monosaccharide, an enantiomer of D-fructose. It is not a common component of foods, but it occurs in low amounts in heat-treated milk products. At the European level, it has been discussed whether or not D-tagatose should be treated as a sweetener, thus requiring authorisation as a food additive. However, the EU Standing Committee on the Food Chain and Animal Health concluded that D-tagatose should be considered as a novel food[1]. In the subsequent assessment procedure, this second opinion is issued by the Novel Foods Unit of the Medicines Evaluation Board Agency, after consultation of the Committee on the Safety Assessment of Novel Foods (VNV Committee).

Initial assessment

The initial assessment of the application for market authorization was carried out by the Advisory Committee on Novel Foods and Processes (ACNFP) of the Food Standards Agency in the United Kingdom. The ACNFP concludes that the information supplied by the applicant sufficiently demonstrates the safety of D-tagatose. Therefore, the ACNFP has no objection to authorisation, if the applicant adheres to the proposed specification. The ACNFP does point out that foods containing D-tagatose must also meet the European labelling requirements for specified food allergens. The ACNFP also expresses its view on labelling of D-tagatose containing foods, with regard to a possible laxative effect of consuming larger quantities of D-tagatose in a single serving, and related to nutrition labelling rules for sugars.

Findings of the VNV Committee

The VNV Committee has no objection to the authorisation of D-tagatose as a novel food ingredient. The committee bases its view on the information in the dossier (see Annex A for the summary) and on the initial assessment by the ACNFP (see Annex B). The committee has also used information from the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2].

The VNV Committee concurs with the opinion of the ACNFP that the production process does not give rise to concern and that the final product is sufficiently specified. The starting material for the production is lactose, which is hydrolysed by the immobilised enzyme lactase

[1] Standing Committee on the Food Chain and Animal Health, Section on Toxicological Safety. Summary report of the meeting of 17 December 2004.
(http://www.europa.eu.int/comm/food/committees/regulatory/scfcah/toxic/agenda16_en.pdf)

[2] Evaluation of certain food additives. WHO Technical Report Series #928, p. 39-42.
(http://whqlibdoc.who.int/trs/WHO_TRS_928.pdf)

to produce galactose and glucose. Subsequently, a fraction containing the galactose is isolated using a cation exchange resin. Galactose is isomerised to D-tagatose by addition of calcium hydroxide. Further purification yields a final product containing at least 98% of D-tagatose. Using HPLC analysis, the only detectable impurity is galactose, formed as a by-product of the production process.

The applicant aims for a global application of D-tagatose in a broad range of foods, and not limited to specific consumer groups. The applicant has provided a list of proposed levels of D-tagatose in different products. The applicant uses these figures in combination with dietary survey data from the United States to estimate the likely consumption of D-tagatose. The ACNFP has combined these data with food survey data from the UK to calculate intake estimates for different age groups (see page 7 of the initial assessment report). Estimates for mean consumption ranged from 2.8 to 5.6 grams per person per day. The highest estimated intake was 11.9 grams per person per day for the 97.5th percentile for 6 to 12 year old children in the UK. The ACNFP notes that higher levels of intake could result from higher levels of D-tagatose in products or a broader range of uses. In the opinion of the VNV Committee, this possibility should be taken into account when this product is authorised.

Since D-tagatose is incompletely absorbed after ingestion, its energy value is lower than that of sucrose. Like the ACNFP, the VNV Committee concludes that this fact is not relevant to the safety assessment. The ACNFP points out that there is a legal requirement to label these products using the higher energy value fur sugars.

The VNV Committee agrees with the conclusion of the ACNFP that the information in the dossier does not give rise to concerns regarding microbiological safety.

The JECFA has performed an extensive toxicological assessment of D-tagatose. The findings of the JECFA are also relevant for this novel food assessment. The JECFA has previously set a temporary Acceptable Daily Intake (ADI), but has allocated an ADI “not specified” after studying additional data in 2004. This means that, on the basis of available data on the properties of this substance and its proposed use, the JECFA sees no hazard to health[3]. The JECFA has taken into account that D-tagatose has physiological and toxicological properties similar to those of other carbohydrates of low digestibility. Like the ACNFP, the VNV Committee concurs with this JECFA conclusion. The JECFA also noted that the ADI “not specified” does not apply to individuals suffering from one of two known rare hereditary disorders of the fructose metabolism. These are fructose intolerance (fructose-aldolase deficiency, incidence 1:20,000) and fructose 1,6-diphosphatase deficiency (incidence unknown)[4]. People suffering from these inborn disorders have no tolerance or a reduced tolerance for fructose. According to the applicant, these people will also react on D-tagatose, but the effect will be reduced due to lower absorption. In the applicant’s opinion, there is no need for a special information statement on the label of foods containing D-tagatose. The ACNFP does not address this issue in its assessment report. The VNV

[3] Principles for the safety assessment of food additives and contaminants in food. (http://www.inchem.org/documents/ehc/ehc/ehc70.htm)

[4] To be distinguished from essential fructosuria (fructokinase deficiency, incidence 1:130,000), which is considered a harmless metabolic abnormality and not a disease.

Committee is of the opinion that it is important for these consumers to be able to recognise products containing D-tagatose.

Data from the applicant indicate that incomplete absorption can lead to a laxative effect in susceptible individuals, when more than 15 grams of D-tagatose is ingested in a single serving. The applicant proposes precautionary labelling of products containing more than 15 grams of D-tagatose per serving. The ACNFP supports this idea for solid foods, but recommends labelling of soft drinks containing more than 1% of D-tagatose.

Conclusion

In summary, the VNV Committee concurs with the conclusion of the first assessment by the ACFP, that D-tagatose can be used safely for the applications described in the dossier. The VNV Committee has noted the relevant issues regarding labelling of D-tagatose containing foods. However, in the Netherlands, labelling issues are discussed separately in the Regular Consultation on the Commodity Act. The committee does want to stress that products containing D-tagatose should be distinguishable as unsuitable for people suffering from some rare hereditary disorders of the fructose metabolism.

De commissie / The Committee

- Prof. dr CAFM Bruijnzeel-Koomen
  hoogleraar dermatologie/allergologie; UMC Utrecht
  professor of dermatology/allergology; University Medical Centre Utrecht
- Ir EJ Kok
  toxicoloog; RIKILT Instituut voor Voedselveiligheid, Wageningen
  toxicologist; RIKILT, Institute of Food Safety, Wageningen
- Dr CF van Kreijl
  moleculair-bioloog; RIVM Bilthoven
  molecular biologist; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr P van der Laan
  emeritus hoogleraar statistiek; Technische Universiteit Eindhoven
  emeritus professor of statistics; Technical University Eindhoven
- Dr FM Nagengast
  gastro-enteroloog; UMC St Radboud, Nijmegen
  gastro-enterologist; University Medical Centre St Radboud, Nijmegen
- Dr ir JMA van Raaij
  voedingsfysioloog; Wageningen Universiteit en Researchcentrum; RIVM Bilthoven
  food physiologist; Wageningen University and Research Centre; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr ir G Schaafsma
  hoogleraar voeding; Wageningen Universiteit en Researchcentrum
  professor of nutrition; Wageningen University and Research Centre
- Dr GJA Speijers
  toxicoloog; RIVM Bilthoven
  toxicologist; National Institute of Public Health and the Environment, Bilthoven
- Prof. dr WJ Stiekema
  hoogleraar bioinformatica; Wageningen Universiteit en Researchcentrum
  professor of bioinformatics; Wageningen University and Research Centre
- Dr JW Tas, adviseur
  Ministerie van VWS, Den Haag
  Ministry of Health, Welfare and Sport, The Hague
- Prof. dr WM de Vos
  hoogleraar microbiologie; Wageningen Universiteit en Researchcentrum
  professor of microbiology; Wageningen University and Research Centre
- Dr RA Woutersen
  toxicoloog, toxicologisch patholoog; TNO Kwaliteit van Leven, Zeist
  toxicologist, toxicologic pathologist; TNO Quality of Life, Zeist
- Dr CMA van Rossum, beoordelaar voedselveiligheid / scientific assessor food safety
  Bureau Nieuwe Voedingsmiddelen, CBG, Den Haag
  Novel Foods Unit, Medicines Evaluation Board, The Hague
- Dr M Rutgers, beoordelaar voedselveiligheid / scientific assessor food safety
  Bureau Nieuwe Voedingsmiddelen, CBG, Den Haag
  Novel Foods Unit, Medicines Evaluation Board, The Hague

Bioresco
Food Scientific and Regulatory Services

D-TAGATOSE

Application submitted on behalf of
Arla Food Ingredients amba, Viby, Denmark, for evaluation
pursuant to Regulation (EC) No 258/97 on novel foods
and novel food ingredients

Executive Summary

Author: Albert Bär PhD

Date: February 9, 2005

Bioresco Ltd. Bundesstrasse 29 CH-4054 Basel Switzerland
Telephone ++41 61 273 77 00 Telefax ++41 61 273 77 03 e-mail: contact@bioresco.ch Internet: http://www.bioresco.ch

D-Tagatose is a monosaccharide and thus a sugar. Its chemical formula corresponds to that of fructose, except for an inversion of the hydroxyl group at C-4. In other words, D-tagatose is an epimer of fructose. Like other sugars, D-tagatose has a sweet taste. Its relative sweetness is about 75-92% that of sucrose. Since the chemical structure of D-tagatose is very similar to that of fructose, its physicochemical properties are also similar. Accordingly, the incorporation of D-tagatose in foods affects their taste, texture and other properties in a similar way as would the incorporation of fructose or other sugars.

Unlike fructose, which is absorbed nearly quantitatively from the human digestive tract, ingested D-tagatose is absorbed slowly and thus incompletely. The metabolism in the human body of the absorbed portion (about 20 - 25%) corresponds to that of fructose, yielding the same end-products. The not absorbed portion (about 75 - 80%) is fermented by the intestinal microflora to short-chain fatty acids (mainly acetic, propionic and butyric acid), i.e. the same products that are formed in the intestine by fermentation of other low digestible carbohydrates, such as lactose ("milk sugar"), raffinose (a naturally occurring trisaccharide) and fructo-oligosaccharides.

D-Tagatose occurs naturally in heat-treated dairy products such as milk-powder, milk-based infant formulae, sterilized milk and yoghurt in small amounts (2-800 ppm). It is formed in these products from galactose by isomerisation at elevated temperature. D-Tagatose was also detected in an exudate of the cacao tree and as an intermediate product of the bacterial metabolism of lactose and galactose.

On a commercial scale, D-tagatose is produced from lactose, a disaccharide consisting of one molecule glucose and one molecule galactose. The production process starts with the enzymatic hydrolysis of lactose, yielding glucose and galactose, followed by isomerisation of the obtained galactose to D-tagatose in the presence of calcium salts at elevated pH. The obtained D-tagatose is then purified by standard techniques including chromatographic fractionation and crystallisation. The final product has a purity of >98%. Considering the purity of the starting material (lactose >99% pure) and the different treatment and purification steps of the production process, it is unlikely that any milk proteins would be present in D-tagatose. This was confirmed experimentally for lactalbumin which could not be detected in D-tagatose by means of an ELISA test.

D-Tagatose is intended to be used in foods primarily as a nutritive substance which, like other sugars, has a sweet taste, and which -in addition- offers the benefits of a reduced energy value, a low glycemic effect, a prebiotic activity and, in confectionery, which does not contain readily fermentable carbohydrates, the benefit of non-cariogenicity.

Considering the nutritional benefits and sensoric properties of D-tagatose, this sugar is expected to be used, for example, in ready-to-eat cereals, health bars, diet soft candies, chocolate-type products, and other inherently sweet foods.

Using US food consumption data and assuming that D-tagatose would be present in all intended applications (except chewing gum and formula diets) at the highest feasible concentration, the two-day average intake has been estimated at about 4.6 and

9.8 g per day for the mean and 90th percentile consumer ("user"), respectively. Expressed in terms of g D-tagatose/kg body weight/day, the highest intake is projected for preschool children with values of 0.19 and 0.37 g/kg bw/d for the mean and 90th percentile consumer ("user"), respectively. For the users of all age groups combined, the estimated intake is 0.08 and 0.19 g/kg bw/d for the mean and 90th percentile consumer. The additional intake from chewing gum is estimated at 0.030 - 0.035 g/kg bw/d for the average user (assuming a use level of 30%). The intake of D-tagatose is evenly distributed over the different daily meals and snacks with an average intake of 3.1 and 6.2 g per eating occasion of the mean and 90th percentile consumer, respectively.

The safety of D-tagatose was examined in a battery of standard genotoxicity tests, a 13-week subchronic toxicity study in rats, an embryotoxiciy/teratogenicity study in rats, and a 2-year carcinogenicity study in rats (modified protocol). In addition, a number of metabolism studies were conducted in rats, pigs and humans.

The intestinal tolerance of D-tagatose was examined in several human studies. At doses of up to 15 - 20 g per eating occasion, flatulence was usually the only observed side-effect. The spectrum of the intestinal symptoms at higher doses and their approximate dose/response relationship are similar for D-tagatose and other incompletely absorbed carbohydrates.

These and other published data have been evaluated by panels of independent qualified experts in the US, the Joint FAO/WHO Expert Committee on Food Additives (JECFA), and Food Standards Australia/New Zealand (FSANZ). All these expert groups concluded that D-tagatose does not present a significant risk to human health under its intended conditions of use. Accordingly, the US-FDA issued on October 25, 2001 a "no-further-question" letter in response to a GRAS Notice of D-tagatose. In Australia/NZ, D-tagatose was authorized as a novel food without limits of use in April 2004. An approval for the use of D-tagatose was also granted in Korea. JECFA allocated an ADI "not specified" at its 63rd meeting in June 2004.

JECFA pointed out that the ADI "not specified" is not applicable to subjects with hereditary fructose intolerance (HFI), a subgroup of the population which should avoid the intake of fructose. HFI is a rare autosomal recessive metabolic disorder with an incidence of between 1 in 12,000 to 1 in 130,000. HFI is caused by a defect in the gene encoding for aldolase B. The symptoms of HFI result from the intracellular accumulation of fructose-1-phosphate (which is osmotically active) and the corresponding sequestration of phosphate which leads to an intracellular depletion of ATP, hypophosphatemia and hyperuricemia due to adenosine mono-phosphate degradation. In view of the similar metabolism of fructose and D-tagatose, it must be assumed that D-tagatose produces the same effects as fructose in HFI subjects.

In a strict, prescribed diet for older HFI children, the fructose intake is limited to 20-40 mg/kg bw/d. In a self-imposed diet according to individual tolerance, fructose

intakes of up to 100-200 mg/kg bw/d may be acceptable for older children and adults. Because of the lower absorption of D-tagatose than fructose (20% vs. 100%), about five-fold higher levels of D-tagatose may be tolerated. The inadvertent consumption of D-tagatose containing foods will, therefore, not expose HFI subjects to a significant health risk.

Like for sorbitol which is incompletely absorbed (about 20%) and which is converted almost quantitatively to fructose after absorption, a special warning statement of the food label is, therefore, not warranted for D-tagatose.

In conclusion, there is a substantial body of evidence to support the safety of D-tagatose under the conditions of its intended use as a food ingredient.

However, intestinal side-effects, including flatulence and stool softening, may occur in susceptible individuals after consumption of more than 10 - 15 g D-tagatose ingested as a single dose. The tolerable total daily dose is a multiple of the tolerable single dose since the intestinal effects are not cumulative over time. A statement that excessive consumption may lead to intestinal disturbance may, therefore, be feasible on the label of foods containing more than 15 g D-tagatose per serving.

ADVISORY COMMITTEE FOR NOVEL FOODS AND PROCESSES

OPINION ON AN APPLICATION UNDER THE NOVEL FOODS REGULATION FOR D-TAGATOSE

Applicant	**Bioresco, on behalf of Arla Foods, Denmark**
Responsible Person	**Dr Albert Bär**
EC Classification	**2.1**

Introduction

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.

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. Its principal purpose is as a carbohydrate source, with purported nutritional effects of non-cariogenicity and as a prebiotic. During preliminary discussions with the applicant, the Secretariat noted that the use of D-tagatose in foods could fall within the legal definition of a sweetener, requiring authorisation under food additive legislation rather than the regulation on novel foods. This issue has been resolved following discussion with the Commission and other MS and the consensus view is that tagatose should be regarded as a novel food ingredient and not as a food additive.

3. This opinion details the safety of this novel ingredient and does not investigate or comment on the perceived nutritional effects that the applicant attributes to its consumption.

I. Specification of the novel food

Information on this aspect is provided on pp 14-16 and pp25-27, Annexes 1, 3 and 4 of the application dossier

4. As an enantiomer of D-fructose, D-tagatose has the empirical formula $C_6H_{12}O_6$ (see Figure 1). An overview of the compositional analyses of D-tagatose and the raw materials used in its production are given in Annex 1, sections 3 and 5. Detailed information on the specifications of raw materials, process chemicals and ion exchange resins are listed in Annex 1.

5. The novel ingredient (NI) is synthesised by enzymatic hydrolysis from lactose with a purity of ≥99%. All chemicals used in the production process are high purity and have low levels of heavy metals (Annex 1). The resulting D-tagatose has a purity of no less than 98%, a lead content no greater than 1 ppm and an ash content of no more than 0.1%.

6. D-tagatose is produced from lactose using a two-step process. In the first instance lactose is enzymically hydrolysed to galactose and glucose. The galactose is then isomerised to D-tagatose at a high pH using calcium hydroxide as a complexing agent.

7. Batch-on-batch variation has been determined by analysis of 6 batches of D-tagatose, produced by the applicant at pilot scale (Annex 4). These indicate a high degree of reproducibility. HPLC data (Annex 4) show that the only detectable impurity in the final product is galactose, which is present as a by-product of the production process.

8. D-tagatose has been evaluated by JECFA[1] on three occasions, most recently in 2004 when it allocated an ADI "not specified"[2]. The detail of the toxicological evaluation by JECFA is discussed later in this paper. The JECFA specification for D-tagatose is given in Annex 3.

Discussion *Members were satisfied with the specification of the novel food.*

II. Effect of the production process applied to the novel food

Information on this aspect is provided on pp 17 – 24 of the application dossier

9. D-tagatose is produced from food-grade lactose by a two-stage process involving enzymatic hydrolysis of food-grade lactose to form galactose, which then isomerises to D-tagatose under alkaline conditions. The applicant has summarised the process on p17 and included a detailed flow diagram (Figure 2).

10. All chemicals used in the production process including the raw material (lactose) and the immobilised lactase (obtained from *Aspergillus oryzae*) are food grade, as are all anti-microbials and column regeneration chemicals.

11. **Process**

    Lactose is first dissolved in hot water and the pH is adjusted, by addition of lactose solution that has been passed through an ion exchange column, to obtain a mildly acidic solution. This solution is then pasteurised before being passed through a column that contains immobilised lactase. This enzyme preparation is widely used throughout the EU. To avoid contamination, the column is regularly treated with a defined anti-microbial solution.

[1] **JECFA**: Joint FAO/WHO Expert Group on Food Additives.

[2] **ADI Not Specified**: Used by JECFA to refer to a food substance of low toxicity which on the basis of the available data, the total dietary exposure necessary to achieve the desired effect, and acceptable background levels in food does not represent a hazard to health.

12. The resultant hydrolysed lactose solution is concentrated by evaporation before being fractionated using a cation exchange resin. The resultant fractions are collected and the galactose-rich fraction retained. This fraction is cooled and the galactose is converted to D-tagatose by addition of a defined amount of $Ca(OH)_2$, which moves the isomerisation equilibrium in favour of the D-tagatose. D-tagatose is precipitated as an insoluble complex with calcium Once this stage is completed the NI is removed and re-dissolved by addition of CO_2 which neutralises the mixture and causes precipitation of the calcium as $CaCO_3$.

13. **Purification**
The NI is purified by filtration, evaporation, demineralisation, and fractionation. These are described in detail on pages 20-22 of the application dossier.

14. The applicant notes that the conditions used to produce the NI are relatively benign and do not favour other reactions that could potentially occur, particularly during the isomerisation of D-galactose. A brief discussion of the potential impurities that could arise as a result of the occurrence of these 'side reactions' is detailed on page 25. None of the compounds described were found in detectable quantities in the end product (Annex 4).

Discussion *Members were content that the production process employed by the applicant does not give rise to concern*

IX. Anticipated intake/extent of use of the novel food

Information on this aspect is provided on pp 33-46 and Annex 6 of the application dossier

15. The applicant intends the NI to be used as a nutritive ingredient in a variety of products. The availability of these products will not be restricted geographically and there are no plans to target these products at particular consumer groups. A list of products and the levels at which D-tagatose is typically expected to be added can be found in the table below:

Food Category	**Proposed food use**	**Added Tagatose (g per 100g of food)**
Baked goods	Cookies	2
	Quick breads	2
	Muffins	2
	Quick bread type	2
	Coffee cakes	2
Beverages	Diet" and "sugar- free" carbonated beverages; non- carbonated Beverages sweetened with low- calorie sweeteners – includes milk-based beverages, juices, juice drinks, teas, and coffee- based Beverages (ready- to- drink, prepared from mix, and dry mix forms)	1
Coffee drinks	Such as cappuccino and latte	1
Frozen milk based desserts, reduced/low fat	Light ice cream	3
	Frozen milk desserts	3
	Low fat and non fat frozen yoghurts	3

	Related frozen novelties	3
Hard candies	Hard candies including regular and dietetic candies	15
Health bars and diet soft candies	Low fat, reduced fat, diet meal, energy or nutrient fortified bars, dietetic soft candies	10
Icings	Icings (or glazes), such as those used on cookies, pastries, brownies, and angel food, chiffon, and pound cakes	30
Meal Replacement / supplement Beverages	Meal replacement beverages, diet meal beverages, nutrient supplement beverages (ready- to- drink, prepared from mix, and dry mix forms)	5g per 240 ml serving (2.08g per 100g)
	Protein drinks, including supplements and diet beverages (ready- to-drink, prepared from mix, and dry mix forms)	1
Milk chocolate	Milk chocolate candies and coatings/coverings	3
Ready-to-eat cereals	All ready-to-eat cereals	3g per 5-55g serving (5-20g per 100g)
Smoothies	Fruit and dairy “smoothie” type beverages	1
Soft/chewy candies	Soft/ chewy candies such as caramels, toffees, taffies, nougats, Creams, fudges, fondant, and fruit- based confectionery (excluding Marshmallows, soft jellies, gummies, panned candies, and liquorice)	3
Chewing gum	Tooth friendly (non-cariogenic) chewing gum	30
Table top sweeteners, low calorie	Sugar substitutes/replacements	1g per serving
Yoghurt	Yoghurt	2

16. The applicant has used dietary survey data to estimate the likely consumption of tagatose in the United States population. These data were taken from the 1994-1996 Continuing Survey of Food Intakes by Individuals (CSFII) on US households and from the 1998 CSFII on children aged 0-9. The data were collected using 24-hour recall interviews for two non-consecutive days and defined according to time and eating occasions. In all cases, it was assumed that all foods or ingredients in each category would contain the NI at the level stated in the table above. A more detailed breakdown and discussion is given in Annex 6 of the dossier. The table below provides a summary of the estimated intake of the NI for US population older than 2 years old:

Summary of the estimated intake of D-tagatose from its proposed food use (excluding chewing gum and food supplements)					
Population	**Age**	**2-day average intake of D-tagatose**			
		g/person/day		**g/kg bw/day**	
		Mean	**90th Percentile**	**Mean**	**90th Percentile**
Children	2-5	3.2	6.2	0.19	0.37
Young schoolchildren	6-12	4.3	8.5	0.14	0.28
Teenagers	13-19	4.7	9.5	0.08	0.16
Adults	> 20	4.8	10.5	0.06	0.14
Total population	> 2	4.6	9.8	0.08	0.19

17. The intake of the NI from sugarless chewing gum was based on the results from a separate US survey carried out in 1995. The results of this survey indicate that the average gum consumption in the US population was 2.5 pieces per day. The equivalent figures for pre-school children and teenagers were 1.6 and 3.0 per day. (Annex 6 Table 26).

18. The applicant states that, for technological reasons related to the production of tablets, the intake of the NI via the consumption of food supplements is unlikely to exceed 3g/person/day. The applicant has not explained the derivation of this figure.

19. In response to a request from the Committee, the Secretariat compared the data obtained from the US dietary survey data with the UK NDNS data. The results, calculated using the closest matching food categories are detailed below. These data show comparable levels of consumption would be seen in the UK population.

Comparison of intake estimates based on US and UK dietary survey data					
US Data (g/person/d)			UK data (g/person/d)		
Age Group	Mean	90th %ile	Age Group	Mean	90(97.5)th %ile
Pre-school (2-5 years)	3.2	6.2	Pre-School (1½ - 4½ years)	2.8	6.9 (10.3)
School Children (6-12 years)	4.3	8.5	School Children (4-18 years)	5.6	11.9 (17.7)
Teenagers (13-19 years	4.7	9.5			
Adults (> 20)	4.8	10.5	Adults (18- 64)	3.7	9.7 (11.6)

Discussion *Estimates of D-tagatose intake for the US and British populations are similar, based on the list of expected uses provided by the applicant. Members noted that higher levels of intake could result in future if the range of uses was expanded or if D-tagatose is incorporated at higher levels.*

XI. Nutritional information on the novel food

Information on this aspect is provided on pp 28-34 of the application dossier

20. **Reduced Energy Value.** Studies described by the applicant indicate that D-tagatose is incompletely absorbed and therefore has a lower energy value compared with sucrose. The applicant refers a number of studies that indicate that the NI has an energy value of 1.5kcal/g. This figure is significantly lower than the value of 4kcal/g that currently applies for the labelling all sugars as specified in the Nutritional Labelling Directive (90/496/EC).

21. **Lower glycaemic impact and prebiotic activity.** A number of studies were described by the applicant in the dossier. These do not have any bearing on the safety assessment of the novel ingredient.

Discussion *Members agreed that the studies provided by the applicant in relation to the efficacy of the novel ingredient were not relevant to the safety assessment. It was noted that current European Community nutrition labelling rules require that sugars are labelled to indicate that they supply 4 kcalories/g. A more appropriate value can only be applied for D-tagatose if the applicant seeks an amendment to the Nutrition Labelling Directive (90/496/EEC).*

XII. Microbiological information on the novel food

Information on this aspect is provided in Annex 4 of the application dossier

22. The production of the NI does not involve the use of micro-organisms. The microbiological purity of D-tagatose is detailed in tables 1 and 2 of Annex 4. These data indicate that the final product is essentially free from microbial contamination

Discussion *Members agreed that the production does not involve the use of a micro-organism and were content that the production process employed by the applicant does not give rise to concern.*

XIII. Toxicological information on the novel food

Information on this aspect is provided on pp p 44-111 of the application dossier

23. **Biochemical Aspects (Absorption, distribution and excretion)**
The applicant presents a number of studies that indicate a variable and incomplete absorption of D-tagatose. One study also details a pronounced increase in the short chain fatty acids in the blood. SCFA's are produced by bacterial fermentation of the unabsorbed NI in the large intestine. The applicant refers to this 'prebiotic' effect as a tangible benefit that can be attributed to the consumption of the NI.

24. Several studies carried out on humans indicate that intestinal side effects, including stool softening, may occur in susceptible individuals after the consumption of more than 15g D-tagatose (ingested in a single sitting). The

tolerable daily dose is a multiple of the tolerable single dose as the intestinal effects are not cumulative over time.

25. **Metabolism**

The applicant has referred to a number of scientific studies that demonstrate that the metabolism of D-tagatose takes place along well defined biochemical pathways. Following an initial phosphorylation step, the metabolism converges with the pathway seen for fructose.

26. **Toxicological studies**

The applicant includes reports from a number of animal studies, which are listed below. The applicant has also conducted four studies indicating a lack of genotoxicity. These studies have also been reviewed by JECFA, which considered D-tagatose three times during 2001-2004. The initial JECFA evaluation of D-tagatose highlighted a number of questions concerning, glycogen deposition and hypertrophy in the liver, and increased serum levels of uric acid.

27. The applicant commissioned a number of additional studies that paid particular attention to these parameters, and following a detailed evaluation JECFA allocated an ADI “not specified” for D-tagatose at its 63rd Meeting in June 2004. The applicant has submitted the same data for novel food approval.

Genotoxicity studies				
Test	**Test system**	**Concentration**	**Results**	**Reference**
Bacterial gene mutation [a]	*S.typhimurium* (TA 1535, TA 1537, TA1538, TA98, TA100); E.coli (WP2uvrA)	100-5000 mg/plate	Negative	Lawlor, 1993; Kruger, 1999a
Chromosomal aberration [a, b]	Chinese hamster ovary cells	1250-5000 mg/ml	Negative	Murli, 1994a; Kruger et al., 1999a
Micronucleus formation [d]	CD-1 mouse bone marrow	1250-5000 mg/bw (p.o.)	Negative	Murli, 1994a; Kruger et al., 1999a
TK-locus mutation [a, c]			Negative	

a) With and without exogenic metabolic activation (rat liver S9 fraction).
b) Treatment time, 7.4h (without activation), 2h (with activation); harvest time 10h
c) Treatment time, 4h
d) Termination 24, 28 and 72h after dosing

Animal studies					
Type of study	**Species (N)**	**Dose level (% of diet or g/kg bw)**	**Results**	**NOAEL (% of diet and/or g/kg bw/d)**	**References**
acute toxicity test	Rats (5M, 5F) Mice (5M)	10g/kg bw (single dose)	no mortality or reaction to treatment	10g/kg bw	Trimmer, 1989
Subchronic (90-d) toxicity study	S-D rats (20M 20F / group)	0,5,10,20% 10% fru + 10% cellulose	soft stool (day 1-3); reduced weight gain in 20% group; increased abs. and rel. liver weights in 10, 15, 20% tag groups, some hypertrophy of hepatocytes in 15, 20% group [a]	5% [c]) [3.7 (F) and 4.1 (F) g/kg bw/d]	Trimmer et al., 1993 Kruger et al., 1999c
Subchronic (29-31 d) study on liver parameters [d]	S-D rats (20M / group)	0,5,10,20% tag	Dose dependent increase of liver glycogen and lower weight [b)]. No ultrastructural (EM) changes of liver tissue except increased glycogen deposition. Slight increased ALAT, ASAT in 20% tag group probably in response	n.d [d)]	Lina et al., 1998 Bar et al., 1999
Subchronic (6-month) toxicity study	Wistar rats (60 F/group)	0, 5, 10% tag, 20% fru, 10% tag + 10% fru Interim kills on day 3, 7, 14, 28, 94, 128 (10F / group)	Only liver and plasma parameters were examined. No increase of liver weight and no histopathological changes [a)] ; no changes of plasma parameters.	10% of diet [5.8 g/kg bw/d (day 1-28); 4.8 g/kg bw/d (day 1-28)]	Lina & de Bie, 2000d
Chronic (24-month) toxicity/carcinogenicity study	Wistar rats	0, 2.5, 5, 10% tag, 20% fru, 10% tag + 10% fru	Examination of organ weights and his topathology limited to liver, kidneys, adrenals and tests (cecum: weight only). Liver enlargement in 10% tag (M), 20% Fru (M), 10% tag +fru (M&F) but no morphological changes. Increased nephrocalcinosis in females of all tag dose groups and in 10% tag (M) and 10% + 10% fru (M). increased incidence of adrenomedullary proliferative	2.5% of diet [< 1 g/kg bw/d]	Lina & Kuper, 2002 Lina & Bar, 2003

			disease in 2.5% tag (M), 5% tag (M & F), 10% (M & F) and 10% + 10% fru (M&F)		
Energy balance study (33-d)	Pigs (2 / group)	0, 20% tag, 20% suc, 10% tag + 10 % suc	No ultrastructural (EM) changes of liver tissues	5 g/kg bw/d	Mann, 1997
Embryotoxicity / teratogenicity study (range finding)	S-D rats (5M / group)	0, 4, 8, 12, 16, 20 g tag/kg bw/d (day 6-15 of gestation)	Soft stool and diarrhoea at 12 g/kg bw. (No adverse effect otherwise).	20 g/kg bw/d (11 g/kg bw/d)	Schroeder, 1994a
Embryotoxicity / teratogenicity study	S-D rats (24M / group)	0, 4, 12, 20 g tag/kg bw/d (day 6-15 of gestation)	Maternal liver weight increased in 12 and 20 g/kg bw group. No morphological changes in liver. No adverse effects otherwise.	20 g/kg bw/d	Schroeder, 1994b; Kruger et al., 1999b

Key: M = Male, F = Female

Abbreviations: tag, D- tagatose; fru, fructose; suc, sucrose; ALAT, alanine aminotransferase; ASAT, aspartate minotransferase; S-D, Sprague-Dawley; n.d., not determined; bw, body weight.

a) Animals killed after overnight fasting
b) Animals killed in the fed condition
c) Based on effects on liver weight
d) Liver weight cannot be used as a basis for determination of the NOAEL since rats were killed in the fed condition (increased weight is partly due to liver glycogen accumulation). D- Tagatose intake was about 11.4 g/kg bw/d at the high-dose level.
e) A series of additional studies on the effects of D- tagatose on liver weight and glycogen accumulation was performed but their results are not shown in this table because toxicological end- points (e.g.,histopathology)were not examined.

Discussion *The novel ingredient has been subject to a number of toxicological studies. The Committee noted the toxicological assessment by JECFA in 2004 and agreed with the expert group that the data did not highlight any toxicologically significant findings, and exhibited properties that were similar to other carbohydrates of other low digestibility.*

Allergenicity and Labelling

Information on this aspect is provided in p 109-110 and Annex 4 of the application dossier

28. The NI is manufactured from crystalline lactose, obtained from cheese whey, which contains protein at levels of up to 0.2%. Recognising the known allergenic potential of milk and derived products, the applicant has demonstrated the absence of whey protein in the NI using an ELISA method. (<10µg protein equivalent / g NI, see Annex 4). The same assay detected protein in 2 (of 3) lactose samples tested.

29. The applicant speculates that the absence of whey protein is to be expected due to the production process, which involves the use of heat-treatment, high pH, ion-exchange resins and activated carbons.

30. In their consideration of the product JECFA concluded that ingestion of 30g or more of the NI may cause gastrointestinal effects in humans. The applicant has also suggested that no warning on laxative effects is necessary for foods listed in the table containing D-tagatose because the maximum intake of D-tagatose would be extremely unlikely to exceed 10g per eating occasion for consumers of any age group (see Table 3 of application dossier). This statement is based on high level US consumption data using figures at the 90th percentile. Estimates using UK NDNS data are similar. The applicant has also acknowledged that the products described in the table are indicative of intended use only, and it would be appropriate to label any foods containing more than 15g of D-tagatose per serving with the statement “excessive consumption may produce laxative effects”. This text is in line with the current requirement for polyols (Directive 96/21/EC) which applies to foods containing more than 10% polyols. The applicant’s proposal will cover all food categories and is based on the intolerance being induced by the amount, rather than concentration. Unlike polyols, tagatose is proposed for certain beverages, where higher levels of intake may be achieved at a lower concentration of D-tagatose.

31. Following a specific request by the Committee, the applicant submitted additional data to demonstrate that the proposed labelling described above was equally applicable to children as well as adults.

Discussion *Members noted that although the applicant provides evidence that the NI is unlikely to contain whey proteins, the product is derived from a milk source. A new amendment (2003/89/EC) to the food labelling directive (2000/13/EC) requires specified food allergens and their derived ingredients to be included in ingredients listing. Milk is a specified allergen and this requirement therefore applies to the novel ingredient, irrespective of the manufacturing process, unless the applicant applies to the Commission for a formal exemption. Members wished to note that it was their*

view that the data provided to demonstrate that the product was free from milk proteins was unlikely to offer sufficient grounds to qualify for an exemption.

Concerning the potential for exerting a laxative effect, the Committee noted the proposal for labelling on the basis of consumption of more than 15g of the NI in a single serving, similar to the labelling requirement for polyols set out in Directive 96/21/EC. There are no data on the effects of tagatose consumption amongst children although young children are known to be generally more prone to diarrhoea, probably because they have a less developed GI tract. The limited data available on other poorly absorbed compounds, such as sorbitol, indicate that pre-school children may be more sensitive than adults and older children. The applicant does not intend the ingredient to be used in foods specially manufactured for young children but it is likely that they will consume general foods that contain D-tagatose, particularly soft drinks. The Committee therefore considered that the labelling criterion proposed by the applicant is appropriate for solid foods, but proposed that all beverages containing more than 1% D-tagatose should also carry the same advisory labelling.

General discussion

32. Members noted that D-tagatose has been subjected to thorough toxicological testing and agreed with the conclusion of JECFA that it is a substance of low toxicity and does not represent a hazard to health.

33. Like other poorly absorbed compounds, D-tagatose may cause mild gastrointestinal effects in high level consumers. The individual doses of D-tagatose associated with these effects is in the range 15-30 grams which is unlikely to be achieved from consumption of the tagatose-containing foods described by the applicant. Nevertheless, the range of uses may be extended in future and Members supported the applicant's proposal to include advisory labelling on any food product that contained in excess of 15g D-tagatose per serving as being adequate to ensure that consumers were advised of the effect of potential gastrointestinal intolerance. To take account of consumption by young children, and because of evidence that poorly-absorbed compounds may exert a greater laxative effect when taken in liquid form, this advisory labelling should also be applied to all beverages containing more than 1% D-tagatose.

34. Members also noted that allergen labelling as defined in amendment 2003/89/EC to the food labelling directive (2000/13/EC*)* will apply to all products that contain the NI, unless the applicant applies to the Commission for a specific exemption to be incorporated into the relevant directive.

Conclusion

35. The Advisory Committee on Novel Foods and Processes is satisfied by the evidence provided by Bioresco on behalf of Arla Foods that D-tagatose is acceptable, subject to the applicant’s adherence to the proposed specification and the labelling requirements described above.

9 August 2005